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Prize Lectures and Biographical Notes

ESE Geoffrey Harris Prize 2020 – Biography
Annamaria Colao

Authored 500+ peer reviewed publications. Her current areas of research include molecular basis and clinical treatment of tumors in the region of the hypothalamus-pituitary and neuroendocrine tumors. Consequences of deficiency and excess of GH and IGF-I on the cardiovascular system. Endocrine consequences in survivors of malignant neoplasia. Insulin resistance and cancer. Secondary osteoporosis. Endocrine consequences of bariatric surgery in obesity. She is affiliated with numerous medical societies, including Italian Society of Endocrinology; Italian Society of Andrology and Sexual Medicine Medical Association Doctors Endocrinologists, Endocrine Society; European Neuroendocrine Association, European Neuroendocrine Tumors; European Society of Endocrinology.

The Geoffrey Harris Prize Lecture
AP1

Abstract unavailable

EJE Award 2020 – Biography
Davide Calebiro

Davide Calebiro is a Professor of Molecular Endocrinology and Wellcome Trust Senior Research Fellow at the Institute of Metabolism and Systems Research (IMSR) and the Centre of Membrane Proteins and Receptors (COMPARE) of the University of Birmingham.

He leads a multidisciplinary research team comprising biologists, chemists, physicists, engineers and computer scientists focusing on the basic mechanisms of G protein-coupled receptor (GPCR) signalling and their alterations in endocrine and metabolic diseases. To study GPCR signalling in cells and tissues, they develop and use innovative optical methods based on FRET and single-molecule microscopy, which allow them to directly observe signalling events in living cells with unprecedented spatiotemporal resolution.

His major scientific contributions include the discovery that GPCRs are not only active at the plasma membrane but also at intracellular sites and that these receptors interact among themselves and with other membrane proteins to form dynamic nanodomains at the plasma membrane.

Davide has published 60 research papers, many of which in prestigious scientific journals, attracting several prizes and awards. He is serving on multiple panels and committees, including the Programme Committee of the Society for Endocrinology and the MRC Molecular & Cellular Medicine Board.

The *European Journal of Endocrinology* Prize Lecture
AP2

Shining light on membrane receptors

Davide Calebiro
University of Birmingham, Birmingham, United Kingdom

G protein-coupled receptors (GPCRs) are the largest family of membrane receptors and major drug targets. They play a fundamental role in the endocrine system by mediating the effects of several hormones and neurotransmitters. Alterations of GPCR signalling, for instance due to genetic mutations, are responsible for a variety of endocrine diseases ranging from congenital hypothyroidism to Cushing's syndrome. My group develops innovative optical methods such as fluorescence resonance energy transfer (FRET) and single-molecule microscopy, which allow us to investigate GPCR signalling directly in living cells with unprecedented spatiotemporal resolution. Using this innovative approach, we are investigating some of the most fundamental mechanisms at the basis of GPCR signalling and their involvement in human disease. This led us to discover that GPCRs are not only active at the plasma membrane, as previously strongly believed, but also at intracellular sites. Moreover, our work has contributed to the identification of new genetic alterations responsible for endocrine diseases, including the recent discovery that mutations in the catalytic α subunit of protein kinase A cause cortisol-producing adrenocortical adenomas. Altogether, our findings indicate that GPCR signalling is much more complex and dynamic than previously thought. This not only has major implications for understanding the functioning of this important family of receptors, but might also lead to the development of innovative drugs for common diseases such as diabetes or heart failure.

DOI: 10.1530/endoabs.70.AP2

European Hormone Medal 2020 – Biography
Olle Kämpe

Olle Kämpe is professor and senior consultant in endocrinology at the Karolinska Institutet in Stockholm, Sweden. He holds the Torsten and Ragnar Söderberg endowment professorship in clinical endocrinology since 2014 and was before that professor of molecular medicine at Uppsala University between 1999 and 2014. He is fellow of the Royal Swedish Academy of Sciences (www.kva.se/en), and member of the Nobel Assembly at the Karolinska Institutet. He was adjunct member of the Nobel Committee for the Prize in Physiology or Medicine 2017-2019 and a member of the Nobel Committee since 2020. He has participated in several EU-projects of which he coordinated one, EurAPS, dealing with APS-1/APECED. He has identified a number of the autoantibodies in clinical use for Addison's disease and APS-1 and initiated the Swedish national registries and biobanks (www.addisonregistret.se) for these disorders.

European Hormone Medal Lecture
AP3

The cause of autoimmune endocrine diseases

Olle Kämpe
Department of Endocrinology, Karolinska University Hospital (Solna), Karolinska Institutet, Stockholm, Sweden

Autoimmune endocrine diseases such as type 1 diabetes and autoimmune adrenal insufficiency (Addison's disease) are disorders that often aggregate in families. Despite being universally lethal before the 20th century, the predisposing genetic variants have remained in the population, probably conferring advantages even at the price of an enhanced risk of developing autoimmunity. With carefully phenotyped patients and geographically matched controls, strong signals can be obtained in genome wide associations studies (GWAS) even with small cohorts in rare diseases. In patients with autoimmune adrenal insufficiency positive for 21-hydroxylase autoantibodies genetic variants of MHC, BACH2 and AIRE have emerged as the most important risk genes.

Monogenic disorders such as Autoimmune Polyendocrine syndrome (APS-1) and Immune Dysregulation Polyendocrinopathy, Enteropathy, X-linked (IPEX) have proved invaluable for our understanding of the events eventually leading to endocrine autoimmunity. These rare syndromes have helped us identify the genes AIRE and FOXP3, critical for important tolerance mechanisms. They also represent good examples of how research on rare disorders translate into novel diagnostic tools and better understanding of more common autoimmune disorders, and at the same time improve clinical care practices for patients with APS-1 and IPEX.

DOI: 10.1530/endoabs.70.AP3

Clinical Endocrinology Trust Award 2020 – Biography
Richard Eastell

I received a clinical fellowship from the Medical Research Council to study osteoporosis at the University of Edinburgh in 1978. I furthered my clinical research training by working at the Mayo Clinic under the supervision of Dr B L Riggs where I worked for five years. I developed a number of new approaches for studying osteoporosis while at the Mayo Clinic including the use of stable (non-radioactive) isotopes to measure the absorption of calcium from food, the use of an infusion technique to measure the production of the active form of vitamin D, the measurement of bone density at the site in the wrist where fractures commonly occur (the ultradistal radius) and a height ratio approach to identifying vertebral fractures on radiographs of the spine. I began my training in endocrinology and diabetes at the Western General Hospital in Edinburgh in 1980 and continued it at Northwick Park Hospital in Harrow in 1982 and at the Mayo Clinic in 1987.

I joined the Department of Human Metabolism and Clinical Biochemistry at the University of Sheffield in 1989 as a Senior Research Fellow. I set up a metabolic bone service at the Northern General Hospital and am an Honorary NHS Consultant. I became Professor of Bone Metabolism in 1995 and received funding from the Arthritis Research Campaign to use biochemical tests of bone turnover to better understand the way in which older men and women develop osteoporosis and propensity to fracture.

My studies on the cause, diagnosis, prevention and treatment of osteoporosis have been conducted with the support of many colleagues; I have supervised the study for 37 doctoral degrees over the past 30 years. I have published over 550 research papers.

I am currently Director of the Mellanby Centre based at the University of Sheffield. I became an NIHR Senior Investigator in 2009. Some of my recent contributions have been authorship on key papers describing new treatments for osteoporosis, such as tibolone, zoledronic acid, denosumab and lasofoxifene as well as addressing issues about safety of medications and provide guidelines to diagnose primary hyperparathyroidism, a common disorder resulting in high levels of blood calcium.

My work as a clinical investigator was recognised in 2014, by the Frederick C Bartter Award from the American Society for Bone and Mineral Research.

Clinical Endocrinology Trust Lecture

AP4

Postmenopausal osteoporosis: balancing the risks and benefits

Richard Eastell
Director, Mellanby Centre for Bone Research, University of Sheffield, Sheffield, United Kingdom

The fractures that result from postmenopausal osteoporosis have a major public health impact. We have a number of drugs we can use to reduce the risk of these fractures. Most of these drugs are anti-resorptive, such as the bisphosphonates (alendronate, ibandronate, risedronate and zoledronate), raloxifene, oestrogen, and denosumab. Until recently the only anabolic agent available was teriparatide. However, in the last couple of years two new agents have been approved in some countries, namely abaloparatide (an analogue of parathyroid hormone related protein) and romosozumab (an antibody against sclerostin). Important questions arise such as should the anabolic drugs be given early in the course of osteoporosis or just to patients with severe disease? What treatment should be given after these anabolic treatments? The anti-resorptive drugs are very safe. However, it has become common practice to take 'drug holidays' in patients taking bisphosphonates for 3–5 years in order to prevent rare side effects such as atypical femur fracture. Thus, the indications for treatment, the order of treatment and the individualisation of treatment are all important considerations for optimal patient care. We highlighted these issues in a recent guideline from the Endocrine Society[1], endorsed by the European Society for Endocrinology.

Reference

1. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH & Shoback D. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology and Metabolism* 2019 **104** 1595–622.

DOI: 10.1530/endoabs.70.AP4

Plenary Lectures

Exercise as Medicine – A Translational Perspective
PL1

Abstract unavailable

Glucocorticoids in Cancer: A New Paradigm
PL2

Abstract unavailable

Harnessing the Microbiome in Metabolic Disease
PL3

Harnessing the microbiome in metabolic disease

Sonia Fernandez Veledo
Head of Diabetes and Metabolic Associated Diseases Research Group, Pere Virgili Institute - Rovira i Virgili University, University Hospital Joan XXIII, Tarragona, Spain

Communication between microbiota and the host is critical to sustaining the vital functions of the healthy host, and disruptions of this homeostatic coexistence are associated with a range of diseases including obesity and T2D. Microbiota-derived metabolites act both as nutrients and as messenger molecules to shape host pathophysiology. Succinate, which has the distinction of being produced by both the host and microbiota, is quickly becoming a poster child for these metabolites. Succinate is a by-product of some bacteria and a primary cross-feeding metabolite essential for the maintenance of a healthy resident gut microbiota. In this sense, the increase in succinate in some pathological conditions would be reflective of dysbiosis. For many years succinate has been considered as a danger signal via its intracellular and extracellular signaling properties. Nonetheless, unexpected pleiotropic functions, such as a positive regulator of intestinal gluconeogenesis and thermogenesis, have been ascribed to this metabolite. In this context, we have demonstrated that succinate via its cognate receptor SUCNR1 is a key mediator of the resolution of inflammation– a physiological mechanism that is not working properly in obesity. Thus, similar to what happens with other hormones as insulin and leptin, obesity and T2D is associated with higher circulating levels of succinate but impaired SUCNR1 signaling, which we have termed a succinate-resistant state. We have also proposed circulating succinate as a surrogate marker of metabolic control and an excellent predictive biomarker for diabetes remission after bariatric surgery. An important unanswered question concerns the source of circulating succinate. Along this line, we recently provided the first demonstration of a close relationship between circulating succinate and gut microbiota signature. To establish the contribution of gut microbiota to circulating levels of succinate as well as the use of probiotic interventions directed to decrease the higher circulating succinate and thus recover the physiological functions of succinate are our current research focus.

DOI: 10.1530/endoabs.70.PL3

Mechanisms for SARS-CoV-2 Cell Entry
PL4

SARS-CoV-2 entry into cells and its inhibition

Stefan Pöhlmann
Infection Biology Unit, German Primate Center – Leibniz Institute for Primate Research, Göttingen, Germany

The coronavirus disease 2019 (COVID-19) has devastating consequences. The establishment of antiviral intervention targeting the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, is urgently needed. However, such approaches require the identification of virus-host cell interactions essential for viral spread and pathogenesis. The viral spike protein (S) mediates the first step in SARS-CoV-2 infection, viral entry into target cells, and is the key target for neutralizing antibodies. In this presentation, I will discuss the cellular factors engaged by the SARS-CoV-2 S protein for entry and will outline strategies for intervention. One focus will be on the S protein activation by host cell proteases. I will discuss why the serine protease TMPRSS2 plays a central role in this process whether auxiliary S protein-activating proteases might impact extrapulmonary spread of SARS-CoV-2. Further, I will discuss how S protein activation can be blocked and whether such strategies are successful in COVID-19 patients.

DOI: 10.1530/endoabs.70.PL4

Maternal Thyroid Hormone and Child Brain Development
PL5

Abstract unavailable

It Takes Thyroid Hormone to Make Sense
PL6

Maternal thyroid hormone and child brain development

Tim Korevaar
Erasmus University Rotterdam and Harvard TH Chan School of Public Health

During this presentation, I will share my views on the effects of maternal thyroid hormone on child brain development. I will discuss the physiology of maternal thyroid function during pregnancy and how this relates to time-dependent processes of fetal brain development. I will also discuss the various aspects of assessing fetal brain development. This is particularly important because we can only assessments fetal brain development in the children after birth, and we have to use proxy measurements such as child IQ or developmental disorders. I will share an overview of recent clinical studies that have used different approaches to identify and quantify the relevance of maternal thyroid hormone for fetal brain development. I will discuss common pitfalls in the setup and interpretation of such studies and share my views on what is needed in the future. Finally, I will discuss the interpretation of current available randomized trials and provide insights into the potential harms associated with levothyroxine overtreatment.

DOI: 10.1530/endoabs.70.PL6

Effects of EDCs on Neuro-Endocrine Systems and Behaviour

PL7

Endocrine disruption of neuroendocrine development, function, and behavior

Andrea Gore
Professor and Vacek Chair of Pharmacology, The University of Texas at Austin, United States

Environmental endocrine-disrupting chemicals (EDCs) are exogenous chemicals that perturb hormones and their actions. Exposures to EDCs during critical periods of life, especially in the developing fetus and infant, are particularly problematic due to the high sensitivity of the perinatal hypothalamus to endogenous hormones and exogenous compounds. Our lab has been using a rat model of prenatal exposure to two classes of EDCs: a polychlorinated biphenyl (PCB) mixture used previously in industry, the fungicide vinclozolin, in current agricultural use, or the vehicle. These chemicals are administered to the dam during the period of prenatal brain sexual differentiation in the developing offspring. These latter female and male rats are phenotyped for effects on development, hormones and behavior in adulthood, and functional behavioral outcomes. Protein, gene expression, and epigenetic changes to the brains of these animals are also determined. Our results show that sociosexual and anxiety-like behaviors are changed by EDCs in a sexually-dimorphic manner. Gene expression profiling of brains from these animals has identified suites of genes differentially affected by EDCs compared to vehicle rats, with sex-, age-, and brain-region specific differences. Recent results have focused on the implications of these changes induced by EDCs for mate choice behavior and underlying neural pathways involved in conveying information about the attractiveness of a mate and transducing it into a behavioral choice. As a whole, our work indicates that gestational exposure to PCBs has lifelong effects on the developing brain, neuroendocrine systems, and reproductive and social behaviors in exposed individuals. These data are highly relevant to humans and wildlife, as all individuals are exposed to environmental chemicals due to their persistence and ubiquity.

DOI: 10.1530/endoabs.70.PL7

Symposia

New Horizons in Phaeochromocytoma and Paraganglioma

S1.1

Abstract unavailable

S1.2

Combination targeted therapies for malignant tumours – towards precision medicine

Svenja Nölting
Specialist in internal medicine, endocrinologu and diabetology, Endocrine oncology, adrenal gland, Medical clinic and polyclinic IV, Munich, Germany

For metastatic phaeochromocytomas (PCCs) and paragangliomas (PGLs), there are currently no highly effective therapies available. We therefore investigated multiple novel molecular-targeted drug combinations in murine PCC cell lines and, most importantly, in human PCC/PGL 2D and 3D primary cultures ($n=18$). Additionally, we analysed signalling pathway alterations as well as somatic mutations in the patients' tumours in order to correlate these data with drug responsivity of individual patient tumours. In a large cohort of 16 human PCC/PGL 2D primary cultures, we confirmed that the mTORC1 inhibitor everolimus in combination with the PI3K inhibitor BYL719 was highly effective at low clinically-relevant doses via strong inhibition of mTORC1/p70S6K signalling and significant attenuation of everolimus-induced AKT activation. Everolimus in combination with other targeted drugs such as the tyrosine kinase inhibitor sunitinib also additively decreased primary culture growth ($n=16$), while combination therapy of BYL719 with the MEK inhibitor trametinib even synergistically decreased PCC/PGL primary culture viability ($n=3$). Additionally, we discovered that the BRAF inhibitor dabrafenib promoted PCC/PGL primary culture survival through a paradoxical MAPK activation ($n=13$). Combination therapy of the HDAC inhibitor entinostat with the PARP inhibitor niraparib showed antagonistic effects in PCC/PGL cultures ($n=15$). In one patient primary culture, extraordinarily high SSTR2 expression was found by Western blot analyses. This patient is currently being treated with SSTR2-guided radionuclide therapy and responded very well to the first 2-cycles. We further verified drug efficacy in human PCC/PGL 3D tumour spheroids and murine PCC cell lines. Moreover, we have engrafted two different human PGL primary cultures into R2G2 immunodeficient mice to serve as relevant experimental models for *in vivo* drug screening of human PCCs/PGLs. Utilising patient-derived 2D/3D primary cultures we have established models to generate highly clinically relevant data, emphasizing combinatorial therapy, providing further insight and evidence for personalised therapy (precision medicine) of PCCs/PGLs.

DOI: 10.1530/endoabs.70.S1.2

S1.3

Abstract unavailable

Osteoporosis and Fracture Prediction

S2.1

Risk of fractures following discontinuation of denosumab – and how to handle it

Bente L Langdahl
Endocrinology and Internal Medicine, Aarhus University Hospital, Denmark

Denosumab (DMAB) discontinuation is characterized by an increase in bone turnover and a rapid bone loss. These changes are associated with an increased risk of multiple vertebral fractures (VFx). Prevalent VFx, longer duration of therapy, greater gain in hip BMD during DMAB, and greater loss of hip BMD after DMAB were identified as risk factors for multiple VFx following DMAB cessation in a retrospective analysis of the FREEDOM Extension Study. Case series have indicated that prior bisphosphonate therapy may mitigate the increase in bone turnover after DMAB discontinuation. Current evidence indicates some efficacy of subsequent antiresorptive treatment depending on the duration of DMAB treatment. The ZOLARM-AB study investigated if transitioning to zoledronate can prevent the bone loss following DMAB discontinuation. The study included 61 patients with osteopenia, discontinuing DMAB after 4.6 ± 1.6 years. Zoledronate was administrated 6 or 9 months after the last DMAB injection or when bone turnover had increased. BMD decreased significantly in all groups. Incident vertebral fractures were seen in two women in the 9 months group. In conclusion: In case of DMAB discontinuation, alternative antiresorptive treatment should be given and the effect monitored using bone turnover markers or BMD. In patients who have been treated for only a few years, oral bisphosphonates for 1–2 years may prevent the bone loss, however, in patients treated with DMAB for a longer period of time, it is recommended to use zoledronate. In patients at high fracture risk continuing DMAB should be considered given the favourable efficacy and safety profile.

DOI: 10.1530/endoabs.70.S2.1

S2.2

Abstract unavailable

S2.3

The role of bone turnover markers in the diagnosis and management of osteoporosis

Elena Tsourdi
Dresden, Germany

During the last years, bone turnover markers (BTMs) have gained importance as surrogate markers to monitor both anti-resorptive and anabolic treatment, and may be used in conjunction with bone mineral density (BMD) measurements in clinical practice. The two most widely utilized BTMs are pro-collagen type 1 N-terminal propeptide (PINP), which reflects osteoblast activity, and C-terminal-cross-linking telopeptide of type 1 collagen (CTX), which corresponds to the osteoclastic function. BTMs can be measured on several occasions in one individual with good precision. However, these markers are subject to several sources of variability; including feeding (resorption decreases) and recent fracture (all markers increase for several months). BTMs are not used for diagnosis of osteoporosis and do not improve prediction of bone loss or fracture within an individual. In people with osteoporosis, BTMs might be useful to evaluate the response to anabolic and antiresorptive therapies, to assess compliance to therapy, or to indicate possible secondary osteoporosis. While prior treatment with bisphosphonates results in smaller BMD and BTMs changes in patients transitioning to denosumab as compared to treatment-naïve patients beginning denosumab therapy, it has also been proposed to blunt enhanced bone turnover and/or attenuate BMD loss after denosumab discontinuation. On the contrary, postmenopausal women switching from teriparatide (TPTD) to denosumab depicted a continued increase in BMD, with bone resorption maximally suppressed after 1-month of denosumab and a delayed suppression of bone formation with maximal effects after 12–24 months of denosumab treatment. More studies are needed to investigate the use of bone turnover markers for assessment of the bone safety of new medications.

DOI: 10.1530/endoabs.70.S2.3

Controversial Issues in Bariatric Surgery

S3.1

Abstract unavailable

S3.2

Abstract unavailable

S3.3

Relapse and prediction of relapse

Erik Stenberg
Department of Surgery, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Background
Over the last decade, bariatric and metabolic surgery has been recognized as an important step in the treatment algorithm for type-2 diabetes (T2DM). Despite early suggestions of surgery providing a potential cure for T2DM, only a small proportion of all patients who could benefit from surgery are ultimately considered for this treatment. Furthermore, the long-term effects on T2DM still remains somewhat controversial.
Methods and results
A review of the current literature as well as data from the Scandinavian Obesity Surgery Registry (SOReg) were considered. Remission of diabetes occurred for 58–89% of patients with T2DM. A higher chance of remission was reported for patients with shorter duration and a less severe disease. Age, surgical method, postoperative weight-loss, sex and socioeconomic status may also influence the chance of reaching remission. Relapse of disease was reported to occur in 19–50% of those who initially experienced remission. Longer duration and a more severe disease, as well as female sex, weight-regain, and type of surgery are associated with higher risk for relapse. Patients who eventually relapse still experience reduction in the risk for diabetes complications.
Conclusion
The chance of reaching diabetes remission after metabolic and bariatric surgery is high. While relapse is common, patients still experience long-term metabolic benefits from this type of surgery.

DOI: 10.1530/endoabs.70.S3.3

Unveiling Signatures in Pituitary Neuroendocrine Tumours

S4.1

Circulating microRNAs: from PitNET pathogenesis to diagnostics

Henriett Butz[1,2]
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Introduction
MicroRNAs are short, single-stranded, protein non-coding RNA molecules which can be secreted into the circulation by mammalian cells. Their altered expression pattern has been described in many different physiological and pathological conditions. In the extracellular compartments they are encapsulated within vesicles, associated to proteins or apoptotic bodies. Due to their stability they are suggested as promising circulating biomarkers. Regarding pituitary adenoma several studies have been published describing the different expression pattern of miRNAs and their role in adenomagenesis on tissue level, but only a few publications investigated circulating miRNAs.
Aim
To identify pituitary tissue-specific miRNAs in circulation comparing tissue and blood miRNA profiles reported in literature.
Methods
Data mining of available serum or plasma miRNAs detected in patients with pituitary adenomas. Reevaluation of expression data and correlation with tumor biology.
Results
Overall, a global downregulation of miRNA expression was reported in plasma samples obtained from patients with pituitary adenoma compared to healthy controls. Pituitary adenoma tissue-specific miRNAs have low abundance in plasma, minimizing their role as biomarkers. To date, only miR-143-3p was reported as plasma maker for non-functioning adenomas which level decreased following surgery.
Discussion
Circulating miRNAs in pituitary adenoma would help patient care especially in non-functioning adenoma as minimally invasive biomarkers of tumor recurrence and progression. However, technical difficulties may challenge the clinical use of miRNAs as potential biomarker and the application of standardized protocols could help their clinical utility. MiR-143-3p may predict tumor recurrence but it needs further investigation.

DOI: 10.1530/endoabs.70.S4.1

S4.2

Abstract unavailable

S4.3

Unravelling the PitNET methyloma

Antonio Pico[1,2]
[1]Department of Endocrinology & Nutrition, Hospital General Universitario de Alicante, Spain; [2]University Miguel Hernández, Spain

Context
Pituitary tumorigenesis does not fit into the most common model of cancer development driven by gene mutations. Instead, epigenetic mechanisms have been widely involved. Among them, aberrant DNA methylation at CpG sites is one of epigenetic hallmarks of tumour cells. There are several methods to study the epigenetic regulation of genome activity, from DNA methylation arrays to more specific DNA methylation analysis such as pyrosequencing, Methylation-Specific PCR (MS-PCR) or MS-multiplex ligation-dependent probe amplification (MS-MLPA) of selected genes.
M & M
We studied the DNA-promoter methylation and gene expression of 35 tumour suppressor genes in 105 pituitary neuroendocrine tumors (PitNETs) by MS-MLPA and quantitative real-time PCR techniques, looking for differences among subtypes and between functional and invasive behaviour of tumors. Moreover, I revised the most relevant results published in the literature.
Results
We observed different methylation patterns among PitNET subtypes. The methylation status correlated negatively with its gene expression in some but not all methylated genes. Moreover, some genes appeared more frequently methylated in macro and invasive tumours than in micro or non-invasive ones. Finally, we found significant differences between functioning and

non-functioning corticotroph tumours. The revision of the literature showed contradictory results related to invasion and functionality, mainly due to the sample studied and the techniques used.
Conclusions
It seems clear that aberrant DNA methylation of several genes play an important role in the behaviour of PitNETs. However, as pituitary tumours come from different cell lineages which can show different patterns of methylation, it is necessary to consider the pituitary subtypes as different entities.
DOI: 10.1530/endoabs.70.S4.3

Hyperthyroidism Across the Lifespan

S5.1

Hyperthyroidism in pregnancy
Stine Linding Andersen
Department of Clinical Biochemistry, Aalborg University Hospital, Denmark

Hyperthyroidism in pregnancy should be adequately managed to prevent maternal and fetal complications. The diagnosing of hyperthyroidism in pregnant women is challenged by the physiological alterations in thyroid function tests. Furthermore, the distinction between gestational hyperthyroidism and the hyperthyroidism of Graves' disease presents a clinical challenge. Graves' disease is an autoimmune disorder associated with the presence of thyroid stimulating hormone-receptor antibodies, and the immunological alterations in and after a pregnancy affect the incidence and the manifestation of the disease. An important clinical focus is on the treatment of hyperthyroidism caused by Graves' disease in women of fertile age who are or may in the future become pregnant. Antithyroid drugs (ATDs) constitute a recognized treatment of hyperthyroidism in non-pregnant and pregnant individuals, and a general risk of side effects is known. Severe side effects such as agranulocytosis and liver failure are in general considered rare, but for the use of ATDs in pregnancy there is an additional concern about teratogenic adverse effects. The initial concern emerged from case reports and case series half a century ago and more recently, large observational studies have added new evidence and quantified the risk of birth defects associated with different types of ATDs. The findings that all clinical available ATDs have been associated with birth defects challenge the clinical recommendations on the treatment of hyperthyroidism in an around the early pregnancy period and have led to considerations on the timing and dosage of treatment as well as the role of maternal thyroid function per se.
DOI: 10.1530/endoabs.70.S5.1

S5.2

Abstract unavailable

S5.3

Hyperthyroidism in adolescents
Marek Niedziela
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The term "hyperthyroidism" is a form of thyrotoxicosis due to inappropriately high synthesis and secretion of thyroid hormone(s) by the thyroid. The leading cause of hyperthyroidism in adolescents is Graves' disease; however, one should also consider other potential reasons such as toxic adenoma (TA) or a toxic multinodular goiter (TMNG), and other rare disorders leading to excessive production and release of thyroid hormones. The term "thyrotoxicosis" refers to a clinical state that results from inappropriately high thyroid hormone action in tissues generally due to inappropriately high tissue thyroid hormone levels. Thyrotoxicosis is a condition having multiple etiologies, manifestations, and potential modes of therapy. By definition, the extrathyroidal source of excessive amounts of thyroid hormones such as iatrogenic thyrotoxicosis, factitious ingestion of thyroid hormone, or struma ovarii does not belong to hyperthyroidism. The etiology of hyperthyroidism/and thyrotoxicosis should be determined. If the diagnosis is not apparent based on the clinical presentation and initial biochemical evaluation, diagnostic testing is indicated. It should include (1) measurement of TRAb, (2) determination of the radioactive iodine uptake (RAIU), or (3) analysis of thyroidal blood flow on ultrasonography. A 123I or 99mTc pertechnetate scan should be obtained when the clinical presentation suggests a TA or TMNG. A question arises whether diagnostic workup and treatment (antithyroid drugs, radioiodine, surgery, others), should be the same in adolescents as in adults, whether there are the same goals of treatment in adolescents as in adults, in females vs. males, in reproductive or post-reproductive age. In this aspect, different treatment modalities may be preferred, to avoid potential risks.
DOI: 10.1530/endoabs.70.S5.3

Adrenocortical Carcinoma

S6.1

Tumor tissue micro-environment in adrenal tumor
Hironobu Sasano, Xing Gao & Yuto Yamazaki
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Recent studies have reported that tissue micro-environment including tumor infiltrating lymphocytes (TILs) as well as neo-angiogenesis played pivotal roles in biological and clinical behavior of various human malignancies. In adrenal neoplasms, TILs are far more frequently detected in cortical than medullary tumors. In adrenocortical adenomas, we have recently demonstrated that enhanced angiogenic chemokines, especially CXCL12, in cortisol producing adenoma (CPA), induced TILs, especially CXCR4 positive T cells, which are involved in removing tumor cells of CPA harboring DNA damages inflicted by excessive cortisol through promoting cell senescence from tumor microenviroment. In adrenocortical carcinoma (ACC), PD-1 receptor and its ligand, PD-L1 have been considered to play pivotal roles in immune checkpoint mechanism and to serve as potential markers responding to immunotherapy in various human cancers. In ACC, however, conflicting results have been reported and recent clinical trials of the agent targeting PD-L1 also provided lukewarm results in terms of therapeutic outcome of ACC patients. In TILs, recent study demonstrated the better clinical outcome in the pediatric ACC patients harboring a high CD8+-CTL count. In our recent study of adult ACC cases, CD8 count was significantly correlated with TILs but also with CD4 and Treg or FOXP3 counts. PDL-1 status in carcinoma cells of ACC , was also significantly correlated with TILs and CD8 counts but also with CD4 count in the tumor and PD-L1 positive carcinoma cells were less than 1% in all 15 cases examined. In pheochromocytoma, results of our recent study in 39 cases revealed that TILs were not as abundant as other malignancies but CD8 counts as well as vascularity examined by CD31 positive endothelial cells served as the prognostic factors in well differentiated pheochromocytoma. In addition, as previously reported, CD68/CD163 positive macrophages appeared to play roles in biological behavior of well differentiated pheochromocytoma.
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S6.2

Circulating microRNAs in the differential diagnosis of benign and malignant adrenocortical tumours
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MicroRNAs, the endogenous mediators of RNA interference have been shown to be helpful as markers of malignancy and prognosis in various neoplasms. The use of microRNAs as biomarkers has been greatly expanded with findings showing their secretion into body fluids (liquid biopsy). Mi-

croRNAs are released both passively due to necrosis and inflammation, and actively in extracellular membrane vesicles (exosomes, microvesicles) or in macromolecular complexes. Circulating microRNA can be determined both from unfractionated plasma/serum samples or from extracellular vesicles.
The preoperative diagnosis of adrenocortical cancer (ACC) is difficult and relies mostly on imaging. The applicability of circulating microRNA for the differential diagnosis of benign and malignant adrenocortical tumours has been investigated in some studies. The most reliable circulating microRNA for the diagnosis of adrenocortical cancer appears to be miR-483-5p. Overexpressed miR-483-5p showed a specificity approaching 100 %, and sensitivity of almost 90 % for ACC diagnosis in different studies on both unfractionated serum and extracellular vesicles. However, miR-483-5p was not significantly different in ACC compared to adrenal myelolipoma. Other microRNAs, such as underexpressed miR-195 might be promising markers. Circulating microRNAs can be exploited for the follow-up of ACC that could be of major clinical relevance. The circulating microRNA expression profiles in cortisol-secreting and hormonally inactive adrenocortical tumours are also different. Circulating microRNA markers for the two major forms of primary aldosteronism (unilateral adenoma and bilateral adrenal hyperplasia) have also been identified. Circulating microRNAs are promising markers, but there are still major differences among the findings on circulating microRNA by different research groups and therefore uniform methodologies and larger cohorts are needed to reduce interassay variability and to increase their reliability.

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S6.3

ACC - what's new today; where is hope tomorrow

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Adrenocortical Carcinoma (Adrenal Cancer or ACC) is a rare malignancy. It requires multidisciplinary care to manage the multiple endocrine and oncologic manifestations of the disease. We will use the recently published international ACC Guidelines to illustrate essential components of the standard of care work-up, diagnosis, and management of ACC. As an understanding of genetics is becoming increasingly mainstream in cancer biology and care including adrenocortical carcinoma (Adrenal Cancer or ACC), we will discuss the burgeoning work in endocrine genetics and current efforts to translate such work into better strategies for diagnosis and for the development of targeted therapies for the treatment of adrenal cancer. Additional goals of this talk are to understand the role of genetics in the pathobiology of adrenal cancer and to discuss how such knowledge is transforming how we care for our patients.

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Endocrine Disruptors, Just a Hype or Not?

S7.1

The environment and male fertility, will we disappear?

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From an evolutionary point of view, reproduction is one of the key events. Thus, any potential threat to human fertility, needs to be taken seriously by researchers as well as the general public. In 1992 a meta-analysis of 63 published papers, indicated almost 50% reduction of sperm counts during the period 1940 to 1990. Since then, the discussion on whether the sperm numbers are decreasing or not has divided the scientific world into believers and non-believers. A concomitant rise in the incidence of testicular cancer and, possibly, even congenital malformations of male genitalia, has been claimed as support to the hypothesis of negative secular trend in male reproductive function. The rapidity by which these changes have occurred has pointed to non-genetic causes – life style changes and/or environmental exposure to so called *endocrine disrupters (ED)*. Whereas animal studies have shown that ED given in sufficiently high doses, may possess a negative effect on male reproduction we are still looking for a "smoking gun" in the context of human exposure. So far, relatively weak associations between exposure to ED – at doses normally found in humans – and semen parameters, have been reported. However, it has been hypothesized that male reproductive organs are mostly vulnerable to the negative effect of ED, during early fetal period. Human studies, linking fetal exposure to male reproductive function are still very scarce and, therefore, not yet conclusive. During the next few years we can expect more robust data based on utilization of several biobanks of maternal blood obtained during early pregnancy. However, recent research has indicated the impaired male fertility may be associated with increased risk of long-term comorbidity including metabolic and cardiovascular diseases, osteoporosis as well as cancer. With up to 40% of men having – from fertility point of view – suboptimal sperm counts, the threat to the human race may not only be related to suboptimal fertility rates but also to reduced life expectance and unhealthy aging.

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S7.2

The bad cocktail of endocrine disruptors

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Several lines of evidence fuel concerns about endocrine disruptors and human health: First, there are increasing trends of endocrine-related disorders such as endocrine cancers, neurodevelopmental disorders, diabetes, thyroidal diseases, and congenital malformations. Second, several widely used chemicals have been linked to such disorders in epidemiological studies and experiments with laboratory animals. Although human exposures involve many endocrine disruptors simultaneously, these efforts have largely focused on single chemicals. Using the example of declines in male reproductive health, this presentation summarises the state of the art of experimental mixture studies with chemicals known to disrupt male sexual development. These studies show that risk assessments should consider combined exposures to bisphenols, polychlorinated dioxins, polybrominated diphenyl ethers, analgesics, parabens, phthalates, triclosan and azole pesticides together. The first mixture risk assessment with focus on declines in semen quality which considers all these chemicals together is presented. It shows that current exposures of the general population are several-fold higher than levels judged to be tolerable. Bisphenols, dioxins and analgesics make the largest contribution to combined risks to semen quality. This analysis calls for substantial reductions in exposures to several chemicals to protect the developing foetus and childhood, life stages vulnerable to impacts on semen quality. It helps prioritise those chemicals that should be targeted to achieve the greatest impact on risk mitigations. The findings provide explanations for reports of substantial declines in semen quality in Western countries.

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S7.3

Micro(nano) plastics, a real threat or not?

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Environmental pollution by microplastics has been transcending usual stakeholders (such as policymakers and scientists) to become a public concern. The conspicuous, widespread occurrence of (micro)plastics together with the publicization by the media of its potential impacts on wildlife and human health have contributed for this state of affairs. Microplastics, typically defined as plastic particles smaller than 5 mm, have been detected throughout the marine, freshwater and terrestrial environment, as well as in many items commonly consumed by/in contact with humans. This pervasive presence makes Human exposure certain (but exposure-dose has yet to be established). Some microplastic fibers and particles are small enough to become internalized and transported within the body. Moreover, they include added chemicals (from the production process) and can act as "chemical sponges" that sequester and, subsequently, release toxic xenobiotics. However, critical data are lacking to accurately estimate human exposure and effects: small sized microplastics (<100 μm) are seldom measured (and some sources are

virtually ignored); the methods for identifying and measuring the particles is highly variable between studies rendering their comparison difficult and leading to under or overestimations; most studies do not identify the polymers present in the analyzed samples, which constitutes a problem since each polymer has different additive chemicals and affinities for contaminants; sample analysis results seldom include mass measurements; studies of human and animal health effects are too few and too limited, and those available test for unrealistic doses; most human exposure media are not sampled, while others are over studied (i.e., seafood ingestion). This leads us to inevitably conclude that, despite the acceleration in scientific research into the effects of microplastics exposure, no broad conclusions toward human health can, at this point, be drawn. However, "absence of evidence is not absence of presence" and further research is binding.

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PCOS: from Genetics to Treatment

S8.1

Abstract unavailable

S8.2

Estroprogestins and female sexuality

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Estroprogestins (EP) are the short-acting hormonal contraceptives most commonly used in Europe, and include combined oral contraceptives (COCs), the patch, and the vaginal ring. Although the safety and efficacy of EP have being extensively investigated, scarce and controversial evidence is available on their impact on female sexuality. The potential negative effects of EP on female mood and desire are hypothesized to derive from sex steroids altering the interplay between neurotransmitters in specific brain areas. Detrimental effects on arousal, lubrication and orgasm have been attributed to changes peripheral concentration in both androgens and estrogens. In fact, EP suppress ovarian synthesis of androstenedione and testosterone and also reduce free androgen levels by increasing the hepatic production of sex hormone binding globulin (SHBG). The progestin component may influence such increase in SHBG, since progestins with androgenic activity induce a less pronounced increase than those with antiandrogenic activity. However, all available EP reduce androgen levels, independently of estrogen dosage and progestin type. As for estrogens, in the last years COCs containing low and very-low doses of ethinyl estradiol have been developed, in order to reduce the risk of side effects, but potentially leading to hypoestrogenism. Despite this strong pathogenetic background, in the vast majority of studies the use of oral EP did not significantly affect sexual desire, whereas data on non-oral forms of EP are scarce. On the other hand, EP seem to change female perception of male attractiveness with a weaker preference for cues of genetic fitness. Low-level evidence also suggests that EP induce a reduction in orgasm frequency. While the effect of oral EP on vaginal lubrication and vulvovaginal atrophy are controversial, no negative effects with the vaginal ring have been reported on these aspects. Finally, oral EP have been associated with an increased risk of painful bladder syndrome.

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S8.3

Current insights into the genetics of polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder, affecting 10–18% of women of reproductive age. Based on the Rotterdam consensus, PCOS is diagnosed by at least two of the following three criteria: oligo- or anovulation, hyperandrogenism, and polycystic ovaries on ultrasound. Thus, four different phenotypes can be recognized. In addition, PCOS is also a metabolic disorder since many affected women present with obesity, insulin resistance and associated metabolic comorbidities. This makes PCOS a very heterogeneous disease and explains why, despite its prevalence, the pathophysiology is still not understood.

Genetic predisposition and environmental exposure are thought to play a major role in the pathophysiology of PCOS. Recent genome-wide association studies (GWAS) in women of Han Chinese and Western European descent have identified several genetic loci associated with PCOS. Importantly, these PCOS-susceptibility loci account for maximally 10% of the estimated heritability, suggesting that there is missing heritability. It will be important to determine whether the different diagnostic criteria for PCOS account for different biological subtypes with a distinct genetic architecture. Studies are ongoing to address this question.

In addition, variants with a lower allele frequency, not detected by GWAS, may contribute to this missing heritability. Recent studies have identified rare PCOS-specific variants in anti-Müllerian hormone (*AMH*) and its receptor (*AMHR2*). This strongly suggests that serum AMH is not only a marker for the polycystic morphology in PCOS, but that aberrant AMH signaling may also contribute to the pathophysiology of PCOS.

In conclusion, the technical advancement in sequencing techniques allows for improved genotype-phenotype studies. Combined with functional studies, this will aid in deciphering the potentially different biological mechanisms involved in PCOS.

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COVID-19 Session

Endocrine Targets Related to COVID Infection
CS1.1

Endocrine targets related to COVID19 infection

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SARS-CoV-2 infection produces greater morbidity and mortality in people with cardiovascular disease, diabetes, and obesity, raising the possibility that the consequences of viral infection are modulated directly and indirectly by the endocrine system. Hospitalization and severity of illness is more common in males, further suggesting that sex, possibly male and female sex hormones, modifies the host response to coronavirus infection. SARS-Co-V-2 cellular infection requires ACE2, as well as associated proteases, including TMPRSS2. These molecules are widely expressed in cardiometabolic organs, and the gastrointestinal tract, and to a lesser extent, in the endocrine and exocrine pancreas. Notably, TMPRSS2 is regulated by sex steroids, and clinical trials are examining whether disruption of steroid control of TMPRSS2 expression might be therapeutically useful in SARS-CoV-2 infection, Viral infection may also modify the host susceptibility to autoimmune disease, through dysregulation of humoral and cellular immunity and cytokine expression. Although SARS-CoV-2 infection has not been associated with widespread endocrine dysfunction beyond that commonly seen with critical illness, case reports of automimmune endocrine disease, including type 1 diabetes, have been described. The use of dexamethasone in severely ill individuals with SARS-CoV-2 prompts evaluation of potential endocrine consequences ensuing from sustained high dose glucocorticoid administration. Herein I will review the endocrine consequences of SARS-CoV-2 infection, highlight key knowns and unknowns, and discuss principles for linking coronavirus infection to disorders of the endocrine system.

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Managing the Cytokine Storm
CS1.2

Abstract unavailable

How Strong is Obesity as a Risk Factor for COVID-19 Patients
CS1.3

How strong is obesity as a risk factor for COVID-19 patients?

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Objective
Specific comorbidities and old age create a greater vulnerability to severe Coronavirus Disease 19 (COVID-19). While obesity seems to aggravate the course of disease, the actual impact of the body mass index (BMI) and the cutoff which increases illness severity are still under investigation. The aim of the study was to analyze whether the BMI represented a risk factor for respiratory failure, admission to the intensive care unit (ICU) and death.
Research Design and Methods
A retrospective cohort study of 482 consecutive COVID-19 patients hospitalised between March 1 and April 20, 2020. Logistic regression analysis and Cox proportion Hazard models including demographic characteristics and comorbidities were carried out to predict the endpoints within 30 days from the onset of symptoms.
Results
Of the 482 patients included in the study, 202 (41.9%) had a BMI <25 kg/m^2, 176 (36.5%) had a BMI between 25 and 29.9 kg/m^2, and 104 (21.6%) were obese (BMI ≥ 30 kg/m^2). In the group with obesity, 20 patients (4.1%) had a BMI ≥ 35 kg/m^2. A total of 18 patients (3.7%) had a BMI <20 kg/m^2. Hypertension and type 2 diabetes were reported in 76 (72.8%) and 27 (26%) patients with a BMI ≥ 30 kg/m^2, respectively. Among patients with obesity, 54 (51.9%) experienced respiratory failure, 38 (36.4%) were admitted to the ICU, 26 (25%) required mechanical ventilation, and 31 (29.8%) died within 30 days from the onset of symptoms. At logistic regression analysis, a BMI between 30 and 34.9 kg/m^2 significantly increased the risk of respiratory failure (OR: 2.32; 95% CI: 1.31–4.09, $P=0.004$), and admission to the ICU (OR: 4.96; 95% CI: 2.53–9.74, $P<0.001$). A significantly higher risk of death was observed in patients with a BMI ≥ 35 kg/m^2 (OR: 12.1; 95% CI: 3.25–45.1, $P<0.001$).
Conclusions
Obesity is a strong, independent risk factor for respiratory failure, admission to the ICU and death among COVID-19 patients. Whereas a BMI ≥ 30 kg/m^2 identifies a population of patients at high risk for severe illness, a BMI ≥ 35 kg/m^2 dramatically increases the risk of death.

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Oral Communications

Adrenal and Cardiovascular Endocrinology

OC1.1

Inhibition of glutaminases as a potential novel treatment for SDHB-associated pheochromocytomas/paragangliomas

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Pheochromocytoma/paragangliomas (Pheo/PGL) are rare neuroendocrine cancers with strong genetic background. Mutations in the *SDHB* subunit of succinate dehydrogenase (SDH) predispose to malignant disease with limited therapeutic options and poor prognosis. Novel prognostic markers and therapeutic targets are required to decrease the high mortality rate. Glutaminases play a crucial role in the metabolism of SDH impaired tumor cells. By using a host of cellular and molecular biology techniques in 2D and 3D cell culture formats we show that the proliferation of rat Pheo cell line PC12 is not affected negatively by the inhibition of SDH either by siRNA directed against *SDHB* or treatment with SDH inhibitors (itaconate and atpenin A5). BPTES, a specific glutaminase-1 (GLS1) inhibitor successfully decreased proliferation of SDH impaired PC12 cells. BPTES also significantly increased the ratio of dead cells in the 3D model of SDH impaired PC12 cell line. The role of GLS1 was assessed in 35 Pheo/PGL tumor tissues. Higher GLS1 expression was associated with lower SDHB expression. In summary, our data suggest that the SDH-associated malignant potential of Pheo/PGL is strongly dependent on GLS-1 expression and glutaminases may serve as novel prognostic and therapeutic targets.

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OC1.2

A Phase III randomized, controlled trial of a modified-release hydrocortisone formulation in the treatment of classic congenital adrenal hyperplasia

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Background
Patients with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21-OHD-CAH) have poor health outcomes due to failure of currently available glucocorticoid preparations to control adrenocorticotropic hormone-driven androgen excess. We investigated whether modified-release hydrocortisone (MR-HC), which mimics the physiological circadian cortisol rhythm, could improve androgen control.
Methods
122 patients with 21-OHD-CAH were randomized to receive either MR-HC or standard glucocorticoid therapy (hydrocortisone, prednisolone, prednisone and dexamethasone). Patients underwent 24-hour profiling of serum 17-hydroxyprogesterone (17-OHP) at baseline and for dose titration at 4 and 12 weeks. The change in mean 24-hour serum 17-OHP standard deviation score (SDS) at 24 weeks was defined as the primary outcome.
Results
Both groups achieved better hormonal control at 24 weeks compared to baseline. The change from baseline in 17-OHP SDS was significantly greater in MR-HC patients at 4 ($P=0.007$) and 12 ($P=0.019$) weeks, but not at 24 weeks. In post-hoc analyses at 24 weeks, a greater reduction was observed in the MR-HC group for the 17-OHP SDS score between 07:00 h and 15:00 h ($P=0.044$) and 17-OHP AUC ($P=0.025$). Good disease control (17-OHP <36 nmol/l (<1200 ng/dl) measured at 09:00 h), was achieved more often in the MR-HC group than the standard glucocorticoid group (90% vs 71%, $P=0.0018$). The variability of 17-OHP over 24 hours was reduced in the MR-HC group compared to standard glucocorticoid therapy ($P=0.0001$). Serum androstenedione 24-hour AUC demonstrated a greater reduction in the MR-HC arm (ratio of geometric LS means of MR-HC divided by standard glucocorticoid: 0.636; 95% CI: [0.450, 0.900]; $P=0.0110$). At 24 weeks, the MR-HC and standard glucocorticoid groups were on similar glucocorticoid hydrocortisone equivalent doses (30 vs 31 mg). There were no safety concerns during the study. There were no adrenal crises in the MR-HC group compared with three (4.9%) in the standard glucocorticoid group. Glucocorticoid stress dosing was reported by 26 patients (42.6%) in the MR-HC group and 36 patients (59.0%) in the standard glucocorticoid group. Resumption of regular menses occurred in 5 patients (4 MR-HC, 1 standard glucocorticoid). The partners of two patients in the MR-HC group became pregnant during the study; one had a history of testicular adrenal rest tissue with documented sperm count improvement on MR-HC.
Conclusion
Six months of MR-HC therapy improved the biochemical control of 21-OHD-CAH in the morning and early afternoon with lower circadian variability and increased patient-reported benefits.

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OC1.3

Tumor microenvironment adipose stem cells modulate adrenocortical carcinoma progression

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The metabolic interplay occurring between the tumor microenvironment and cancer cells may represent a potential target for novel anti-cancer approaches. Among stromal components, adipocytes and adipose precursors have been shown to actively participate in tumor progression in several solid malignancies. In adrenocortical carcinoma (ACC), a rare endocrine neoplasia with a poor prognosis, cancer cells often infiltrate the fat mass surrounding the adrenal organ, enabling a possible crosstalk with the adipose cells. The molecular biology underlying adrenocortical carcinoma (ACC) development and growth remains to be fully elucidated.
We set up an *in vitro* co-culturing system to study the effects of human white adipose stem cells (ASCs) on the ACC H295R cell line, in order to investigate the role of the adipose microenvironment on ACC evolution. Cell proliferation rate significantly increased in both ASCs (2.6-fold, $P<0.001$) and H295R cells (1.4-fold, $P<0.005$) after 9 day co-culture compared to the mono-culture condition, with a parallel increase in glucose uptake (2.1-fold, $P<0.001$ and 1.2-fold, $P<0.001$, for ASCs and H295R respectively).
When co-cultured with ASCs, H295R cells showed a significant increased cell migration rate (1.8-fold, $P<0.05$ at 48 hours) and expression of migration-related protein (i.e. FAK, RhoA and Fascin-1), as well as a higher invasion ability (1.6-fold, $P<0.001$). A reciprocal influence of the two cell types was further demonstrated by assessing H295R cells ability to influence ASC differentiation, resulting in a significant decrease in the expression of stem genes, such as Bmi1, Nanog and Oct-4 (2.8, 3.1 and 1.3-fold, respectively) and an increased expression of the myofibroblast-like marker α-SMA. Furthermore, *in vitro*-induced differentiation of ASCs in the presence of H295R cells resulted in an impaired adipocyte maturation, as indicated by the significant decrease observed both in the expression of specific markers, such as Adiponectin, FABP4 and HSL (0.28, 0.25 and 0.27-fold, respectively) and intracellular lipid content (0.58-fold, $P<0.001$).

In conclusion, our results support the occurrence of a specific crosstalk between ACC and its adipose microenvironment, leading to cancer cell reprogramming associated with increased invasiveness, opening new perspectives for the development of more effective therapeutic approaches.
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Keywords: adipose precursors, adipogenesis, invasion, cancer, cell reprogramming.
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OC1.4

Immune infiltrate and PD-1 / PD-L1 expression in adrenocortical carcinoma: who can predict patients´ outcome?

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Context
Adrenocortical carcinoma (ACC) are endocrine malignant neoplasms associated with severe aggressiveness. Tumour-related glucocorticoid excess occurs in 60% of patients and is associated with poor prognosis. First clinical trials using immune checkpoint inhibitors are quite unsatisfactory and treatment advancements are urgently needed.
Recently, we characterized tumour-infiltrating lymphocytes (TILs) in ACC and identified the detrimental dependency of immunosuppressive effects of glucocorticoids. In this study, we analyse the impact of the checkpoint markers programmed-death 1 (PD1) and its ligand PD-L1 on patients´ outcome and treatment response as additional factor on resistance to immunotherapy.
Methods
We performed immunofluorescence analysis quantifying the expression of the checkpoint marker PD-1 and PD-L1 in 58 primary ACC. Furthermore, we correlated its presence with clinical data.
Results
Most ACCs show infiltrates of T-cells (86.3%, 7.65 cells/HPF) both cytotoxic (84.3%, 5.70 cells/HPF) and helper cells (74.0%, 6.68 cells/HPF) and Tregs (49.3%, 0.75 cells/HPF). Interestingly, the $CD3^+$, $CD4^+$ and $CD8^+$ ACC-infiltrating immune cells were associated with better overall survival (HR for death: 0.45, 95% CI : 0.25–0.87, $P=0.016$; 0.47; 95% CI : 0.23–0.67, $P=0.001$; 0.39; 95% CI : 0.26–0.85, $P=0.013$; respectively). Moreover, T helper cells were negatively correlated with glucocorticoid excess in localized, non-metastatic ACC and even in local recurrences and metastases ($P=0.049$ and $P=0.006$; respectively). In addition, 36% of ACC show intra-tumoral expression of PD-1 positive tumour-infiltrated lymphocytes (15 ± 30 cells/HPF), while 83% (34 ± 82 cells/HPF) of ACC tumour cells were positive for PD-L1. Interestingly, all tumours with PD-1/PD-L1 expression correlated with immunosuppressive glucocorticoid excess and thus were in the poor prognosis group characterized by immune depletion.
Conclusion
First, tumours of ACC patients are characteristically infiltrated by $CD3^+$, $CD4^+$ and $CD8^+$ T cells that positively influence patients' overall survival. However, ACC were less infiltrated by $CD4^+$ T cell in presence of glucocorticoids. Second, ACC tumours often have increased, but heterogeneous expression of immune checkpoint molecule PD-1/PD-L1 on tumoural and infiltrating immune cells predominantly under glucocorticoid excess conditions. Hence, examine the molecular checkpoint markers considering glucocorticoid secretion may be an option in order to predict patients´ outcome and treatment response to immunotherapy.

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OC1.5

The utility of salivary cortisol and cortisone measurement in the assessment of cortisol secretion in adrenal incidentalomas

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Backgound
Adrenal incidentalomas (AI) are lesions that are incidentally identified while scanning for other conditions. The European Society of Endocrinology guidelines recommend that all patients with AI should undergo an overnight dexamethasone suppression test (ONDST) for the evaluation of autonomous cortisol secretion as defined by failure of suppression of cortisol to <50 nmol/l. The reported prevalence of this is high (50% of patients in a recent publication) and may be linked to an increase risk of cardiometabolic complications in these patients. The ONDST requires attendance to a health care facility and venepuncture. Cortisol and cortisone measurements can also be taken on salivary samples which can be easily collected and posted to the laboratory offering convenience to the patient. We therefore aimed to assess the utility of these measurements in patients with AI.
Methods
We retrospectively analysed the data of 112 patients with AI who underwent an ONDST with measurement of post dexamethasone (0900 h) serum cortisol and salivary cortisol and cortisone and serum and salivary cortisol and salivary cortisone at around midnight the night before. Both serum and salivary samples were analysed with liquid chromatography-tandem mass spectrometry. Statistical analysis was done using SPSS.
Results
There were 64 female and 48 male patients mean age 64, 31 with bilateral adenomas. 48 (43%) failed to suppress there cortisol to <50 nmol/l. There was a strong correlation between salivary cortisone and serum cortisol post 1 mg dexamethasone (R^2 Linear 0.907). No correlation was observed between, serum and salivary cortisol post dexamethasone, or midnight salivary cortisol and cortisone and serum cortisol post dexamethasone.
Discussion
In an ONDST for AI patients, post dexamethasone, salivary cortisone correlates very strongly with serum cortisol and could therefore be used as an alternative sampling method in the ONDST as a simple test (when available) for the evaluation of cortisol secretions in patients with AI which does not require venepuncture or attendance to hospital. We have demonstrated that the prevalence of autonomous cortisol secretion in patients with AI is high and is in line with data that has been reported in the literature recently.

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OC1.6

Modified GRAS score for prognostic classification of adrenocortical carcinoma: an ENSAT multicentre study

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Background
Adrenocortical carcinoma (ACC) has an aggressive but heterogenous behaviour. ENSAT stage and Ki67 proliferation index are used to predict clinical outcome but are limited in distinguishing patients with best outcome. We aimed to validate the prognostic role of clinical and histopathological parameters alone or combined by applying a previously proposed points-based score (mGRAS, Lippert JCEM 2018) to a large multicentre cohort of ACC patients.

Methods
International multicentre retrospective study including ACC patients who underwent adrenalectomy from 2010–2019. Acquired covariates include age at diagnosis, presence of steroid- or mass-related symptoms, ENSAT stage, tumour resection status, Ki67, progression-free survival (PFS), and disease-specific survival (DSS). Each parameter's prognostic value was tested by univariable analysis and PFS and DSS were the primary and secondary endpoints, respectively. Additionally, we evaluated the prognostic performance of mGRAS calculated as follows: age (<50 yr=0; ≥50 yr=1), symptoms (no=0; yes=1), ENSAT stage (1–2=0; 3=1; 4=2), resection status (R0=0; RX=0.5; R1=1; R2=2), and Ki67 (0–9%=0; 10–19%=1; ≥20%=2 points), generating four mGRAS groups: 0–1, 2–3, 4–5, and 6–9. Survival curves were plotted via the Kaplan-Meier method. The discriminative performance of mGRAS and its components were compared using the Harrell's C-index and Royston-Sauerbrei's R^2_D statistic.
Results
We screened 1075 patients from 14 centres; 946 patients met the inclusion criteria (median age 50 years; 61.9% females). Univariable cox regression showed that mGRAS and its components significantly influenced both PFS and DSS. With PFS, mGRAS showed superior prognostic discrimination (C-index 0.71, R^2_D 0.29) compared to its components: symptoms (C-index 0.57, R^2_D 0.08), ENSAT stage (C-index 0.67, R^2_D 0.21), resection status (C-index 0.60, R^2_D 0.18), and Ki67 (C-index 0.65, R^2_D 0.21). mGRAS divided the cohort into four groups with median PFS of 181.6, 33.0, 9.8, and 6.0 months. Similarly, with DSS, mGRAS showed superior discrimination (C-index 0.76, R^2_D 0.44) compared to symptoms (C-index 0.60, R^2_D 0.15), ENSAT stage (C-index 0.72, R^2_D 0.35), resection status (C-index 0.64, R^2_D 0.25), and Ki67 (C-index 0.68, R^2_D 0.31). Median DSS for the mGRAS groups were 248.8, NR, 66.0, and 18.1 months.
Conclusion
The prognostic performance of mGRAS is superior to that of individual clinical and histopathological parameters. This simple score will be valuable in guiding personalised treatment decisions in patients with ACC, e.g. the need for adjuvant mitotane and frequency of monitoring.

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OC1.7

Comparative proteomic analysis of different bilateral adrenocortical hyperplasia

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Bilateral Adrenal Hyperplasias (BAH) are responsible for approximately 10% of ACTH-independent Cushing syndrome and are classified as either micronodular or macronodular. Whereas Primary Pigmented Nodular Adrenocortical Disease (PPNAD) and isolated Micronodular Adrenal Disease (iMAD) are two types of micronodular hyperplasia, Primary Macronodular Adrenal Hyperplasia (PMAH) is a macronodular BAH. These tumors are classified differently based on clinical, histological and genetic features but they all share a dysregulation of the cyclic AMP/protein kinase (PKA) pathway, a molecular signaling system that is essential for the synthesis and secretion of glucocorticoids. We investigated the molecular differences between the various types of BAHs using a proteomic approach on normal tissue, iMAD, PPNAD and PMAH. In total, we identified 37 proteins differentially expressed between these diagnostic groups. Most of these proteins are involved in metabolism and mitochondrial function, which is consistent with prior transcriptomic data as well as the secretory status of BAH. We are currently comparing all "-omics" for consistency and/or important differences. Interestingly, each BAH (iMAD, PPNAD and PMAH) has its own proteomic signature and can be separated by primary component analysis highlighting differences in molecular pathways. We propose that the 37 proteins identified here may provide new clues for the formation of these neoplasms, how they link to the PKA pathway, and importantly assist in their clinical diagnosis.

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Bone and Calcium

OC2.1

Real-life clinical study: 1-year of treatment with burosumab of children and adolescents affected with X-linked hypophosphatemia

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Background/Aim
X-linked hypophosphatemia (XLH) is a rare disease caused by *PHEX* mutation, leading to elevated FGF23, renal phosphate wasting, hypophosphatemia, insufficient $1,25(OH)_2D$ synthesis. Clinically, it manifests with rickets including leg deformities, poor growth, dental abscesses, craniosynostosis, and hearing loss. Beyond conventional treatment (phosphate supplements+active vitamin D), burosumab is pathogenetic anti-FGF23 therapeutic approach, whose efficacy was demonstrated in clinical trials on 1−12 years-old children affected with XLH. Here, we prospectively assessed the efficacy and safety of burosumab on a large cohort of children in clinical practice, including adolescents ≥13 years of age at moment of treatment.
Patients/methods
57 XLH-children (36 girls/21 boys; 9.1±8.9 years; including 10 adolescents ≥13 year-old, 14.5±1.2 years) were switched from conventional therapy to burosumab.
Objectives
The primary end-point was the change from baseline (M0) to 12 months (M12) in the rachitic lesions evaluated through knee MRI by measuring of the maximum width of physis and the transverse extent of widening. The secondary end-points were the changes in biochemical (serum phosphate (sP), TmP/eGFR, ALP, $1,25(OH)_2D$, PTH), clinical parameters (height-SDS, function evaluated through 6-minutes walking test [6MWT]), incidence of dental-hearing-neurological manifestations and safety (incidence of any adverse events, nephrocalcinosis, hyperparathyroidism). In France, the target sP was >1.2 mmol/l (>3.7 mg/dl).
Results
1-year treatment with burosumab significantly reduced the disease activity, as shown by reduction of the transverse extent of widening and the maximum width of medial physis by 50% and 44% (M0→M12: 62±34 → 31±20%; 5.5±2.1 → 3.2±1.4 mm, $P=0.00$ for all, respectively). This was associated with significant reduction in ALP (M0 → M12: 418±150 → 299±146U/l, $P=0.006$) and improvement in physical ability expressed as age-adjusted 6MWT-SDS (M0 → M12: −3.3±1.3 → −2.8±1.3, $P=0.03$). As expected, we found a rescue of phosphate wasting (M0→M12:sP 0.73±0.12 → 1.19±0.15 mmol/l, TmP/eGFR 0.62±0.12 → 1.07±0.17) and $1,25(OH)_2D$ synthesis (M0 → M12: 25±15 → 79±22 pg/ml); $P=0.00$ for all. There were no significant changes in height-SDS and incidence of complications after 1 year. The most common side effects were bone-muscular-abdominal pain, headache, reactions at sites of injection. Adolescents showed higher baseline PTH levels, however, upon burosumab, PTH reduced overtime (M0 → M6 → M12: PTH 85±43 → 57±27 → 66±39 ng/l, $P=0.7$). Secondary hyperparathyroidism in adolescents was associated to a slower restoration of phosphate metabolism.
Conclusion
Our findings on efficacy and safety of burosumab confirm those of clinical trials. Restoration of phosphatemia and endogenous calcitriol synthesis by

burosumab leads to healing of rickets, reduction of disease activity and improvement of physical function. XLH-adolescents show slower restoration of phosphate wasting under burosumab likely due to secondary hyperparathyroidism; noteworthy, the use of burosumab seems to control PTH in adolescents.

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OC2.2

STOPFOP: A european phase II clinical trial using saracatinib to prevent FOP

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Background
Fibrodysplasia ossificans progressiva (FOP) is a rare, genetic and devastating disease characterized by progressive heterotopic ossifications (HO) in muscles, tendons, ligaments and fascia. The formation of HO leads to severe contractures and early death. There are no approved medications yet. The STOPFOP team identified AZD0530 (saracatinib) as a potent, low nanomolar inhibitor of the mutant ALK2 kinase which is the unique genetic driver of this rare bone disease. AZD0530 was proven to be effective in representative FOP mouse models. The European Union's Innovative Medicines Initiative (IMI) has provided funding to investigate the repurposing of this drug, originally designed for ovarian cancer treatment, to treat patients with FOP.
Methods
This is a phase 2a study, designed as an European multicentre 6-month double blind randomized controlled trial (RCT) of AZD0530 vs placebo, followed by a 12 month trial comparing open-label extended AZD0530 treatment with historical control data. In total 20 FOP patients, aged 18 to 65 years, will be included with the classic FOP mutation (R206H). Endpoints are objective change in heterotopic bone volume measured by low-dose whole body computer tomography (CT) , [18F] NaF PET activity and patient reported outcome measures (PROMS).
Discussion
Drug repurposing – using existing clinical molecules for new disease indications - presents an ideal solution for limiting risks in early clinical studies where there is a supporting genetic rationale for the drug in question. This is especially useful in rare diseases, as the study population is limited. Using existing assets and investments, may also allow more affordable pricing once an indication is approved. AZD0530 would represent a rapidly translatable therapy for FOP, having the significant advantage of extensive safety data from over 28 registered clinical trials with AZD0530 involving over 600 patients. Trial registration EudraCT number 2019-003324-20

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OC2.3

Prediction algorithm for persistent primary hyperparathyroidism after parathyroidectomy

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Background
Primary hyperparathyroidism (PHPT) is characterized by an excessive secretion of the parathyroid hormone (PTH) with normal or high calcium levels. The gold standard therapy involves minimally invasive parathyroidectomy with intraoperative PTH (ioPTH) monitoring. Different criteria have been identified when predicting cure rates using ioPTH values.
Objective
To evaluate the percent ioPTH drop (ΔioPTH), the post-excision ioPTH, the first post-operative day PTH/calcium ratio and their possible combinations to predict persistent PHPT (PPHPT) after parathyroidectomy.
Methods
We retrospectively analyzed 211 patients who underwent parathyroidectomy with ioPTH for Primary hyperparathyroidism between 2008 and 2017 at the Department of Otolaryngology of S. Orsola Policlinic of Bologna. Vienna Criteria were used to evaluate the PTH drop during the procedure. By ROC curve we calculated ΔioPTH cut-off, the post-excision ioPTH cut-off, the first post-operative day PTH/calcium ratio cut-off. We compare these values with the Vienna Criteria.
Results
At the last follow-up, 16.4% of patients had normocalcemic PPHPT (NormoPPHPT) and 6% had hypercalcemic PPHPT (HyperPPHPT). ΔioPTH < 69.7% was associated with PPHPT with 66.7% sensitivity and 67.5% specificity. A post-excision ioPTH value ≥55 ng/ml was associated with PPHPT, with 80.0% sensitivity and 77.0% specificity. A first post-operative day PTH/calcium ratio ≥3.58 was associated with PPHPT, with 62.5% sensitivity and 79.8% specificity. PPHPT was more effectively identified with the combination of ΔioPTH < 69.7% and ioPTH post-excision ≥55 ng/ml than with the Vienna Criteria (Area under curve, AUC, 0.832 vs 0.620; $P < 0.001$). When added to the combination, the first post-operative day PTH/calcium ratio slightly but not significantly improved AUC (0.916; $P = 0.187$).
Conclusions
ΔioPTH < 69.7% and post-excision ioPTH ≥55 ng/ml combined are able to predict PPHPT and show a better accuracy than the Vienna Criteria. The combination can thus be a useful tool in post-surgical PHPT follow up.

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OC2.4

Loss of glucocorticoid rhythm induces an osteoporotic phenotype in mice

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Introduction
Glucocorticoid (GC)-induced osteoporosis is a widespread problem that is accompanied with increased fracture risk. Currently, it is unknown whether detrimental effects of GC therapy on bone are simply the consequence of supraphysiological GC doses, or whether absence of the endogenous GC rhythm also plays a role. In this study, we aimed to elucidate the importance of the presence of a diurnal corticosterone (CORT) rhythm, the primary GC in mice, for bone quality.
Methods & Results
We implanted female C57Bl/6J mice with slow-releasing corticosterone (CORT) pellets to blunt the rhythm in CORT levels without inducing hypercortisolism. Flattening of the CORT rhythm for 7 weeks reduced cortical and trabecular bone volume (−8%; $P < 0.001$ and −26%; $P < 0.05$, respectively), as determined by micro-CT analysis. Furthermore, tartrate-resistant acid phosphatase (TRAP) levels were increased (+42%; $P < 0.01$) while procollagen type 1 N-terminal propeptide (P1NP) levels were decreased (−37%; $P < 0.001$) in plasma of mice with a flattened CORT rhythm, indicative of a negative balance in bone remodeling. Double calcein labeling of bone *in vivo* revealed a reduced bone formation, as reflected by a reduced mineral apposition rate (−20%; $P < 0.05$), mineralizing surface per bone surface (−23%; $P < 0.05$) and bone formation rate per bone surface (−39%; $P < 0.01$). Collectively, these perturbations in bone turnover and structure decreased bone strength and stiffness (−15%; $P < 0.01$ and −11%; $P < 0.01$, respectively), as determined by mechanical testing.
Conclusion
We demonstrate for the first time that flattening of the GC rhythm results in an osteoporotic phenotype in mice. Our findings indicate that at least part

of the fracture risk associated with GC therapy may be the consequence a disturbed GC rhythm, rather than an excess in GC dose alone. Thus, reintroduction of a trough and/or peak in GCs could be a promising novel strategy to prevent GC-induced osteoporosis.

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OC2.5

Effect of nine months of vitamin D supplementation on areal and volumetric bone mass density and bone architecture in graves' disease: a double-blinded, randomized clinical trial

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Background
Vitamin D is important to skeletal health and is standard care in conditions with low BMD. Thyrotoxicosis caused by Graves' disease (GD) leads to increased bone turnover and reduced BMD. We aimed to test the hypothesis that vitamin D supplementation would improve bone recovery in GD.
Methods
Using a double-blinded design, hyperthyroid patients with a first time diagnosis of GD were randomized to supplementation with vitamin D3 70 mg/day or placebo as add-on to standard therapy with anti-thyroid drugs (ATD). At baseline and nine months, we measured bone mass density, body composition and bone architecture using DXA and HRpqCT. Between-group differences in change and response to ATD treatment were analyzed using linear mixed modelling. In subanalysis, we tested for interaction between the intervention and baseline vitamin status (insufficient (<50 nmol/l or replete). (The DAGMAR study clinicaltrials.gov #NCT02384668).
Results
86 GD patients were included (86% females, mean age 41 ± 14). Compared with placebo, nine months of vitamin D3 did not significantly improve bone density or architecture. However, vitamin D3 tended to reduce gain in lean body mass (−24%, $P=0.08$), fat mass (−49%, $P=0.21$) and body weight (−33%, $P=0.09$). Vitamin D3 did not affect changes in plasma levels of thyroid hormones or TRAb. In response to ATD, BMD increased significantly in hip 2% (95% CI : 1–4). Cortical porosity decreased, tibia −7% (95% CI : −12 to −2) and radius −14% (95% CI : −24 to −3), and trabecular thickness increased, tibia 5% (95% CI : 2–9) and radius 4% (95% CI : 1–7). Stiffness and estimated failure load did not change significantly. Lean body mass increased 10% (95% CI : 8–12). In subanalysis of all outcomes, the effect of intervention did not differ between patients with a baseline insufficient as opposed to replete vitamin D status.
Conclusion
In newly diagnosed GD, nine months of high dose vitamin D3 supplementation does not offer benefit in improving skeletal health but may adversely affect restoration of body composition. Treatment of thyrotoxicosis is of major importance to restore bone density and microarchitecture.

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OC2.6

Superior efficacy of calcifediol soft gelatin capsules vs cholecalciferol independently of bmi, for the management of vitamin d deficiency in postmenopausal women: a treatment to be considered in therapeutic guidelines

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Background
Vitamin D deficiency is a worldwide health issue that affects more than one billion people. Few guidelines assess optimal dosing of vitamin D in general population, and although there is no international consensus, the optimum dosing for vitamin D3 and mainly calcifediol is not known.
Objective(s)
To assess the efficacy of calcifediol in the treatment of vitamin D deficiency, compared with therapeutic guidelines recommendations for cholecalciferol in postmenopausal women.
Material and Methods
Phase III–IV, double blind, randomized, controlled, multicentre superiority clinical trial approved by the corresponding Ethics Committees and Health Authorities. Postmenopausal women with baseline levels of 25(OH)D < 20 ng/ml were randomised to calcifediol 266 µg /month for 4 or 12 months (standard and test regime), or to cholecalciferol 25 000 IU/month (as per therapeutic guidelines) for 12 months. Results from an interim analysis - performed upon completion of month 4 visit by 100% of evaluable patients - are presented and reported without unblinding subjects' study treatments. Both calcifediol groups are summarised for analysis.
Results
298 women were included in the ITT analysis. All demographic characteristics were balanced amongst groups. Regarding analysis based on World Health Organization classification for BMI (kg/m^2), 41.3% were obese, 32.6% were overweight, 25,2% were normal weight and 1% were underweight. Due to limited sample size, underweight group is not considered for analysis. When treatments are compared for BMI groups at Month 4, mean change versus baseline and % subjects achieving 25(OH)D > 30 ng/ml resulted statistically significant (Table 1). When analysing per treatment group,13.5% and 35% of women in the calcifediol group reached 25(OH)D > 30 ng/ml at 1 and 4 months when compared to 0% and 8.2% respectively in the cholecalciferol group ($P<0.001$). No relevant safety issues reported for the present analysis.

Table 1

	NORMAL		OVERWEIGHT		OBESE	
	Calcifediol ($n=58$)	Cholecalciferol ($n=17$)	Calcifediol ($n=59$)	Cholecalciferol ($n=38$)	Calcifediol ($n=80$)	Cholecalciferol ($n=43$)
Mean Change (ng/ml)	16.6*	12.6	15.6***	9.8	13.4***	8.9
% Subjects with 25(OH)D > 30	51.7*	17.6	33.9**	7.9	25**	4.7

*$P<0.05$; **$P<0.01$; ***$P<0.001$.

Conclusions
Calcifediol shows a greater efficacy than cholecalciferol (as recommended in therapeutic guidelines), for the treatment of vitamin D deficiency in postmenopausal women independently of their BMI. A significant percentage of patients on cholecalciferol group failed to reach recommended levels.
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OC2.7

Surgery alone or surgery in combination with postoperative zoledronic acid for the treatment of osteoporosis in primary hyperparathyroidism: a 2-year double-blind randomized placebo-controlled study

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Background
Osteoporosis is common in primary hyperparathyroidism (PHPT). It is also an indication for parathyroidectomy in PHPT. Bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (DXA) increases after successful surgery. Alendronate significantly increases BMD in PHPT patients not undergoing surgery. It is not known whether surgery alone or in combination with postoperative zoledronic acid more efficiently improves bone health in PHPT.
Objective
To compare the effects of surgery alone with surgery in combination with zoledronic acid on bone turnover and BMD in PHPT.
Methods
Randomized, double-blind, placebo-controlled study of PHPT patients with osteoporosis including DXA and bone marker measurements at baseline, 1- and 2-year follow-up.
Patients
1–3 months after parathyroidectomy, 56 patients with PHPT were randomized to zoledronic acid (ZOL; f/m (25/3), mean age 67.9 yrs) or placebo (PBO; f/m (22/6), mean age 69.0 yrs).
Results
BMD significantly improves 2 yrs after parathyroidectomy, with significantly better scores at the femoral neck (FN) and lumbar spine (LS) in the ZOL compared to the PBO group (Z-score in FN; $P=0.045$ and T- and Z-scores in LS; $P=0.039$ and 0.017, respectively). Bone turnover markers (P1NP, CTX, ALP) decrease significantly more in the ZOL compared to the PBO group ($P<0.001$ for all markers). Of the 18 patients who before surgery had received bisphosphonates for >1 yr, BMD improved significantly in the femoral neck and lumbar spine in the ZOL ($n=10$; $P<0.001$–0.01 for all) but only in the lumbar spine in the PBO ($n=8$, $P=0.03$) group.
Conclusion
BMD increases after parathyroidectomy both with and without zoledronic acid. However, BMD improves significantly more when combined with postoperative zoledronic acid.

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Diabetes, Obesity, Metabolism and Nutrition

OC3.1

Twenty-two years results of the israeli-georgian program diabetes in pregnancy

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Background
The Israeli-Georgian Program Diabetes in Pregnancy was initiated at the Georgian Diabetes Center in 1997, with the aim to provide care for women with diabetes. The Program has become possible as a result of Twinning between Union of Diabetes and Endocrine Association and Israeli Diabetes Association. It was initiated in 1997, and since then it successfully works, being the longest and most sustainable Twinning program in Europe. The aim to assess the efficacy of treatment in women with pre-GDM and GDM.
Methods
In total, 407 women with type 1 preexisting diabetes (mean age 23+6 yrs, diabetes durations 12.4+7.5 yrs) and 119 women with gestational diabetes (GDM) were enrolled in the study. The patients were divided into 4 groups (Gr.):
Gr.1 – 223 patients who received specialized pre-conception care;
Gr.2 – 118 patients enrolled in the program at < 10 weeks of gestation;
Gr.3 – 66 patients enrolled in the program at > 10 weeks of gestation;
Gr.4 – 119 women with GDM.
Results
At entry HbA1c(%) levels for Gr.1, 2, 3 and Gr.4 were: 8.12 (0.05), 9.08 (0.6), 8.09 (1.6), 6.7(0.9) respectively; By the end of preconcetion care HbA1c levels in Gr.1 – 6.0(0.65)% were statistically lower in Gr.2 and 3 ($P=0.000$). By term HbA1c levels statistically decreased in all the groups ($P=0.024$, $P=0.000$, $P=0.000$, respectively). The rate of spontaneous abortions was lower in Gr.1 (2.24%), than in Gr.2 (8.4%) $P=0.000$. In Gr.1 patients percent of pre-eclampsia (0.44%) was lower, than in Gr.2 (8.4%) and Gr.3 (10.6%) (P1 – 2 = 0.0005; P1 – 3 = 0.0002). No statistical difference between Gr.1 and Gr.4 was revealed. In Gr.1 patients percent of preterm deliveries was lower, than in Gr.2 and Gr.3 (P1 – 2 = 0.0014; P1 – 3 = 0.0001). No statistical difference between Gr.1 and Gr.4 was revealed. In Gr.1 patients percent of macrosomia was lower, than in Gr.2 and Gr.3 (P1 – 2 = 0.0074; P1 – 3 = 0.0101); and in Gr. 1 and 4 (10.47 – 11.7%) – no statistical difference was observed. Perinatal mortality was observed in Gr.1 – 1.79%, in Gr.2 – 4.23% in Gr.3 – 7.5% and in Gr.4 – 1.68% (P1-2 = 0.0944; P1 – 3 = 0.0129; P1 – 4 = 0.7265).
Conclusion
In patients with Pre-GDM and GDM good glycemia control during pregnancy significantly reduces the risk of spontaneous abortions, pre-eclampsia, preterm delivery, and perinatal deaths. This program shows that proper approach to pregnancy management in diabetes can be successfully implemented even in low-to-middle income countries.

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OC3.2

Influence of obesity in the miRNome landscape: miR-4454, a tissue-specific regulator of insulin response

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Obesity is a major health problem commonly associated with severe comorbidities, including insulin resistance and type 2 diabetes mellitus (T2DM). Emerging evidence suggests that production and secretion of certain micro RNAs (miRNAs) are dysregulated under adverse metabolic conditions and might exert a key role in the development and progression of different metabolic-related pathologies. However, the alteration of the plasma miRNA profile under obesity condition and its pathophysiological implication in insulin resistance and T2DM has not been fully explored. Here, we aimed to explore the dysregulations of the miRNome landscape in human obesity and to unveil the putative role/association of key altered miRNAs with basic clinical characteristics in obesity. Specifically, an Affymetrix-miRNA 4.1 array was implemented in a pilot cohort of plasma samples from normoweight and obese patients (BMI < 25 vs >30), and the main changes were further validated in two independent cohorts of patients ($n=221/n=20$). Moreover, different *in vitro* (using cell models derived from metabolic-tissues) and *in silico* approaches were performed. Our results demonstrated a profound dysregulation in the human miRNome under obesity conditions. Interestingly, miR-4454 was consistently elevated in plasma of obese patients compared to control patients in all the cohorts, and was positively associated with key clinical parameters related to insulin resistance (i.e. insulin levels, HOMA-IR and HbA1b). We found that miR-4454 is mainly expressed in liver and prostate tissues. Consistent with this, *in vitro* treatment with high-dose of insulin induced an overexpression of miR-4454 in liver and prostate cell-line models (HEPG2 and RWPE-1, respectively). Moreover, forced overexpression of miR-4454 led to a marked downregulation in the expression of insulin response-related genes (i.e. *INSR*, *IRB*, *GLUT4)* and to a reduction in the activity of key proteins involved in insulin-signaling pathways (i.e. AMPK and AKT). Additionally, miR-4454 overexpression resulted into a clear alteration of several key splicing factors and spliceosome components associated with the development of T2DM (i.e. *ESRP1*, *ESRP2*, *RBM45* and *RNU2*). Finally, our data showed that bariatric surgery and the treatment with anti-diabetic/obesity drugs (biguanides or statins) led to a reduction in plasma level of miR-4454, which is consistent with a putative role and implication of miR-4454 in obesity. Altogether, our results suggest that miR-4454 could be considered as a novel diagnostic and/or therapeutic target for obesity and its associated comorbidities such as insulin resistance and T2DM.

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OC3.3

Circulating follistatin predicts type 2 diabetes risk

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Follistatin is a hepatokine found to be elevated in patients with type 2 diabetes (T2D) and promotes hyperglycemia in mice. We report that elevated baseline circulating follistatin levels predict future T2D incidence in longitudinal cohorts including up to 5274 individuals. Individuals with elevated circulating follistatin had higher risk of developing type 2 diabetes during follow-up of 4 years (IMI-DIRECT-METSIM, $n=1079$, Finland), 5 and 19 years (MDC-CC, $n=4195$, Sweden). The hazard ratios (HRs) for incident T2D adjusted for multiple risk factors by quartiles of follistatin were 2.26 (95% CI: 0.98-5.22; P for trend=9.00E-16) for 4 years; 4.22 (95% CI: 1.38-2.94, P for trend=0.012) for 5 years; and 1.36 (95% CI: 1.06-1.74, P for trend=0.014) for 19 years. K-means clustering on 4-year follow-up cohorts (IMI-DIRECT and its four sub-cohorts, in total $n=1701$, Denmark, Finland, Sweden and the Netherlands) identified a fast glycemia progression subgroup with higher follistatin and C-peptide levels. Circulating follistatin, adipose tissue insulin sensitivity and liver fat content were studied in a TDFS cohort ($n=210$, Germany); and follistatin levels associated significantly with adipose tissue insulin resistance and circulating follistatin was elevated in non-alcoholic fatty liver disease (NAFLD). In human stem cell-induced adipocytes, follistatin dose-dependently attenuated insulin-inhibited lipolysis and increased free fatty acid release. To identify genetic factors that influence plasma follistatin levels, genome-wide association studies (GWAS) was performed on MDC-CC ($n=4239$), and identified 13 genetic variants, including rs780094 ($P=1.11E-11$), rs780093 ($P=1.91E-11$) and rs1260326 ($P=2.77E-11$) in strong linkage disequilibrium (LD) within the glucokinase regulatory protein (*GCKR*) gene to be associated with plasma follistatin. The results were replicated on SUMMIT-VIP cohort ($n=885$, UK, Italy and Sweden). Regulation of follistatin production in liver cells by GCKR in addition to insulin and glucagon was confirmed in HepG2 cells *in vitro*. Thus, we present a new aspect and mechanism in the development of type 2 diabetes (T2D) which involves hepatokine follistatin. Elevated circulating follistatin predicts T2D, and may predispose to diabetes risk and NAFLD by promoting adipose tissue insulin resistance and adipocyte free fatty acid release. Liver follistatin secretion is regulated by insulin, glucagon and GCKR. Our study suggests that follistatin predicts and mediates type 2 diabetes, and play an important role in the pathogenesis of T2D.

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OC3.4

Dietary intake of fat and oil are associated with expression of miR-143 and miR-34a in visceral and subcutaneous adipose tissues: A nutriepigenetic study

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New evidence indicated that miRNAs may contribute to the regulation of energy balance and metabolic homeostasis, by controlling a wide range of metabolic pathways. miR-143 and miR-34a are the best studied among the miRNAs linked to adipose tissue regulation. Dietary intake, among many other environmental factors, is a key player that can induce epigenetic changes. The aim of the study was to investigate the association of the miR-143 and miR-34a expression in visceral and subcutaneous adipose tissues with habitual fat and oil intakes. Visceral and subcutaneous adipose tissues were obtained from 97 subjects (41 non-obese, 18 obese, and 38 morbid obese), who underwent open abdominal surgery with minimal impact on dietary intake. Intake of hydrogenated and non-hydrogenated vegetable oils and butter were collected by using a valid and reliable food frequency questionnaire. The expressions of miR-143 and miR-34a in visceral and subcutaneous adipose tissues were analyzed by Real-Time PCR. Linear regression models were used to estimate the association of dietary hydrogenated and non-hydrogenated vegetable oils and butter intake with miR-143 and miR-34a expression after adjustment for potential confounding variables. The gene expression of miR-34a was more increased in morbid obese than obese subjects in both subcutaneous (13.3 vs 11.3, $P<0.002$) and visceral (13.4 vs 9.2, $P<0.001$) adipose tissues. There was no association of the miR-143 and miR-34a expression in both adipose tissue in total population. After adjustment for total energy intake, insulin, triglycerides, and age, visceral adipose tissue miR-143 gene expression was positively with total fat and oil intake ($\beta=0.334$, $P=0.024$) in the total population. The expression of miR-143 in visceral adiposity among morbid obese participants was negatively associated with non-hydrogenated vegetable oils ($\beta=-0.317$, $P=0.036$), and directly associated with butter ($\beta=0.503$, $P=0.002$) intake. The miR-34a expression among morbid obese participants was associated with total fats and oils ($r=0.534$, $P<0.001$) and non-hydrogenated oil ($\beta=0.443$, $P=0.008$) in visceral adipose tissue. Moreover, we found significant association of miR-143 expression in subcutaneous adipose tissue with butter in both morbid obese and non-obese participants. An increase in miR-143 and miR-34a expression by total fats and oils, may explain development of obesity through high fat diet. A decrease in expression of miR-143 by non-hydrogenated oils would justify a lower adipogenic capacity and, would therefore contribute to the decrease of fat stores observed in adipose tissue with higher intake of fatty acids contains of non-hydrogenated oils.

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OC3.5

Supplementation with Bifidobacterium breve BR03 and Bifidobacterium breve B632 favoured weight loss and improved insulin metabolism in children and adolescents with obesity in the BIFI-OBESE cross-over, randomized placebo-controlled trial

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Background
Variations in gut microbiota might impact metabolic functions like caloric intake and energy expenditure leading to body weight excess. Microbiota modulation may be a potential approach for obesity management, especially in subject characterized by specific microbial enterotypes.
Objective
We aimed to assess the impact of probiotic treatment in obese children and adolescents, under diet control, on weight loss, glucose, and insulin homeostasis, gut microbiota composition and SCFAs.
Methods
This was a cross-over, double-blind, RCT on 100 children and adolescents (6–18 years) affected by obesity with insulin-resistance (NCT03261466). The subjects on dietary training were randomized to treatment with 2×10^9 CFU/AFU/die of *Bifidobacterium breve* BR03 (DSM 16604) and *Bifidobacterium breve* B632 (DSM 24706) or placebo for 8 weeks with a 4-weeks wash-out period. Clinical, biochemical and stool sample analyses were carried out at each time (T0–T3).
Results
At baseline, there were no differences in clinical and metabolic parameters between treatment and control group, except *Escherichia coli* concentration, which was higher in the placebo group. A mixed-effect model analysis revealed a carry-over effect on most of the variables, suggesting that the probiotic treatment had a prolonged effect over the washout period. Due to this event, only the results of the first phase (T0–T1) were deeply analyzed. For all the subjects (active and placebo) we observed significantly decreased BMI, BMI Z score, waist circumference (WC), systolic and diastolic blood pressure, insulin after OGTT, and *E. Coli* concentrations at T1. Probiotics further decreased WC (–3.51 cm, $P<0.05$), BMI Z score (–0.17 kg/m^2, $P=0.07$), fasting insulin (–4.57 mcUI/ml, $P=0.06$), HOMA IR (–1.1, $P<0.05$), *E. Coli* concentrations ($P<0.02$), and increased nearly

to significance insulin sensitivity after OGTT. No differences were observed in inflammatory cytokines and GLP-1 levels at fasting. Of twenty-five SCFAs, probiotics decreased the 2-methyl- propanoic acid relative abundance ($P<0.02$). The PCoA analysis of SCFAs allowed defining four clusters of patients. Two clusters identified subjects that were healthier and had better responses in BMI Z score, WC, insulin resistance and sensitivity during probiotics.
Conclusions
Probiotic supplementation with *B. breve* BR03 and B632 has determined beneficial effects on weight and insulin metabolism in obese children and adolescents undergoing dietary training. Moreover, the microbiome-host configuration could be a predictor of the obesity phenotype and the efficacy of treatment with *B. Breve* strains.

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OC3.6

11β-Hydroxysteroid dehydrogenase type 1 inhibition protects against the development of adverse metabolic and bone effects of prednisolone: A randomized, double-blind, placebo-controlled trial

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Glucocorticoids (GC) are commonly prescribed, but their use is associated with significant adverse metabolic and bone effects. 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) regenerates active GC within tissues, tightly controlling the availability of GC to bind and activate the GC receptor; Our preclinical data have shown that 11β-HSD1 knock out mice resist the adverse effects of exogenous GC excess. We have now conducted a randomized, double-blind, placebo-controlled clinical study to determine if pharmacological inhibition of 11β-HSD1 (using AZD4017) can prevent the adverse effects of prescribed GC without compromise to their anti-inflammatory actions.
30 healthy male volunteers (age; 38±12 years, BMI; 25.2±2.3 kg/m^2) were recruited and underwent metabolic assessments including a 2-step hyperinsulinemic euglycemic clamp incorporating stable isotopes to measure glucose and fatty acid flux and adipose tissue microdialysis. Immune-inflammatory responses were measured using an OX40 (CD134) assay. All participants received prednisolone 20 mg once daily for 7 days, and, in addition, were randomized to treatment with either AZD4017 (400 mg twice daily) or matched placebo. After 7 days, all investigations were repeated. The primary endpoint was assessed using a general linear model adjusting for baseline measures. Secondary endpoints were assessed using Wilcoxon (paired), and Mann-Whitney (unpaired) tests, where appropriate.
The predefined primary end-point (change in glucose disposal (Gd)) was threefold lower in the AZD4017 group, but this failed to reach statistical significance (–0.58±2.12 vs –1.56±1.99, AZD4014 vs placebo $P=0.17$). As expected, prednisolone+placebo worsened metabolic phenotype; Gd decreased ($P=0.004$), circulating triglyceride ($P=0.018$) and glycerol levels ($P<0.0001$) increased, as did adipose tissue interstitial fluid glycerol release ($P=0.011$). Osteocalcin (as an index of bone formation) also decreased significantly ($P<0.0001$). In contrast, when prednisolone was co-administered with AZD4017, there were no significant changes in any of these variables. Importantly, the OX40 (CD134) assay demonstrated a robust response to prednisolone (1.4±0.3 vs 0.6±0.2%, $P=0.011$), which persisted in the prednisolone+AZD4017 treated group (1.1±0.3 vs 0.6±0.1%, $P=0.016$). Circulating prednisolone and prednisone levels were not different between the 2 groups.
We have demonstrated that 11β-HSD1 inhibition limits the adverse metabolic and bone effects of prednisolone. Oral prednisolone (an *'active'* GC) is reliant upon tissue-specific regeneration (from inactive prednisone) for many of its biological actions and these appear independent of circulating levels. In addition, we have provided the first clinical evidence to show that 11β-HSD1 inhibition has potential as a strategy for selectively limiting the adverse side effects of prescribed GC.

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OC3.7

Efficacy and safety of volanesorsen for the treatment of metabolic complications in patients with familial partial lipodystrophy: results of the BROADEN study

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Introduction
Familial Partial Lipodystrophies (FPLD) are rare genetic disorders characterized by marked loss of subcutaneous fat from the extremities with variable fat loss from the face and trunk. Patients with FPLD develop metabolic abnormalities including hypertriglyceridemia, insulin resistance, and diabetes mellitus, which are difficult to manage with conventional therapies including fibrates, statins and insulin. The BROADEN study evaluated the efficacy and safety of volanesorsen, an antisense inhibitor of apolipoprotein C-III, to improve the metabolic abnormalities of patients with FPLD consuming a low-fat diet.
Methods
BROADEN was a 52-week phase 2/3 study of volanesorsen in 40 patients (11 males, 29 females) with FPLD, randomized 1:1 to weekly administration of volanesorsen (300 mg) or placebo. Enrollment criteria included FPLD by genetic, familial or phenotypic criteria; fasting plasma triglycerides ≥2.3 mmol/l (200 mg/dl) and diabetes mellitus. The primary efficacy endpoint, mean percent change in fasting plasma triglycerides from baseline, was evaluated at 3 months and other secondary endpoints were evaluated at 12 months.
Results
The median age of the participants was 49 years (range 28 – 68), and they had a BMI of 29.8 kg/m^2 (range 21.0 – 44.2), fasting plasma triglycerides of 8.6 mmol/l (range 2.4–60.4) and HgbA1c of 8.2 % (range 4.8–10.5) at baseline. Volanesorsen treatment resulted in an 88% reduction in fasting plasma triglycerides as compared to 22% reduction in placebo-treated patients ($P=0.0009$) and this reduction remained significant for the entire duration of the study. As compared to placebo, volanesorsen treatment significantly reduced hepatic fat fraction at 12 months (+1.5% vs –51.9%, respectively; $P=0.004$) but did not improve HgbA1c levels (–0.2% vs 2.3%, respectively; $P=0.77$). The most common adverse event for volanesorsen-treated patients was injection site reactions, which were predominately mild in severity. While reductions in blood platelet count were seen in volanesorsen-treated patients, no one developed severe thrombocytopenia (platelet count <50,000/mm^3). Five patients treated with volanesorsen discontinued treatment due to a mild or moderate adverse event, while no patient on placebo treatment discontinued treatment.
Conclusions
In patients with FPLD, as compared to placebo, volanesorsen therapy results in significant reductions in serum triglycerides and hepatic fat fraction but glycemic control remains unchanged. The prevalence of side effects of volanesorsen was comparable to that reported previously in patients with familial chylomicronemia syndrome, but without any reports of severe thrombocytopenia.

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Pituitary and Neuroendocrinology

OC4.1

Quantitative mRNA expression of PROK2, DUSP6, and WDR11 in peripheral blood as diagnostic criteria for central hypogonadism

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Central hypogonadism (CH) is a syndrome that can be diagnosed in women with hypoestrogenic amenorrhea and a lack of normal response of gonadotropins to hypoestrogenemia in the absence of other reasons. To date, about

50 genes were reported as a possible reason for this condition, but the genetic basis is still unknown for approximately a half of CH cases.
Patients and methods
Some of the CH-related genes are expressing in leukocytes of peripheral blood: *GNRHR* and *GNRH1* (necessary for the adequate biological effect of GnRH); *PROK2* and *CHD7* (responsible for the GnRH neurons migration), *WDR11* and *DUSP6* (involved in normal sexual development). 15 female patients with CH (age from 18 to 50 y.o.) were examined; 6 of them have amenorrhea I and the rest 9 – amenorrhea II. Risk factors of amenorrhea II were: stress, excessive physical exercises, rapid weight loss, past use of oral contraceptives. The control group: 21 healthy women (age from 19 to 37 y.o.) with the regular ovulatory menstrual cycle, some of them have children. A quantitative determination of mRNA expression of genes *GNRHR*, *GNRH1*, *PROK2, CHD7*, *WDR11* and *DUSP6* was completed in the fresh peripheral blood sample by PCR in real-time. Measurement results were normalized to the reference primer beta-actin expression.
Results
Expression patterns of examined genes differed from normal in each case of CH. Changes in neurodevelopmental genes *PROK2*, *DUSP6* and *WDR11* expression were statistically significant: $U_{emp}=75$ vs $U_{cr}=83$ for *PROK2*, 77 vs 88 for *DUSP6* and 66 vs 77 for *WDR11* ($P<0.05$ for all genes; Mann-Whitney U-test). After ROC-analysis diagnostic clipping points were determined: *PROK2* expression >0.009356 and *DUSP6* expression >0.01478 showed sensitivity 60.0% and 60.0% and specificity 82.0% and 83.3%, respectively, for CH diagnosis. *WDR11* expression > 0.002224 pointed to the central genesis of hypogonadism with sensitivity 66.7% and specificity 75.0%.
Conclusion
According to our results, quantitative mRNA expression measurement of neurodevelopmental genes *PROK2*, *DUSP6*, and *WDR11* (which are responsible for CH) can be considered as diagnostic criteria for central hypogonadism with sensitivity 60.0%, 60.0%, 66.7% and specificity 82.0%, 83.3%, 75.0% respectively.

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OC4.2

Both ghrelin deletion and unacylated ghrelin overexpression preserve muscles in aging mice

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Sarcopenia, the decline in muscle mass and functionality during aging, might arise from age-associated endocrine dysfunction. Indeed, muscle wasting follows the general decline in trophic hormones and the establishment of a chronic mild inflammatory status characteristic of aging. Ghrelin is a gastric hormone peptide circulating in both acylated (AG) and unacylated (UnAG) forms that have anti-atrophic activity on skeletal muscle. AG is the endogenous ligand of the growth hormone secretagogue receptor (GHSR-1a), and it is involved in metabolic regulation and energetic balance through induction of appetite, food intake, and adiposity. UnAG does not induce GH release and has no direct effects on food intake, but it shares with AG several biological activities on cell types lacking AG receptor. In particular, both AG and UnAG have direct biological activities on skeletal muscle, including promotion of myoblast differentiation and protection from atrophy, in all likelihood by activating a common receptor. Also, UnAG promotes muscle regeneration, stimulation of muscle satellite cell activity, and activates autophagy and mitophagy at higher extent than AG in muscles of nephrectomyzed mice. Age-dependent hypoghrelinemia could participate in the establishment of sarcopenia by facilitating the progression of muscle atrophy and limiting skeletal muscle regeneration capability. Here, we show that both the deletion of the ghrelin gene (Ghrl KO) and the lifelong overexpression of UnAG (Tg) in mice attenuated the age-associated decline in muscle mass and functionality, seen as larger myofiber areas, lower levels of Atrogin-1, an increased mitochondrial functionality compared to old WT animals. Also, both Ghrl KO and Tg animals displayed reduced systemic inflammation and maintenance of brown adipose tissue functionality. While old Tg mice apparently preserved the characteristics of young animals, Ghrl KO mice features deteriorate with aging. However, young Ghrl KO mice show more favorable features compared to WT animals that result, on the whole, in better performances in aged Ghrl KO mice. Altogether, the data collected suggest that, in Ghrl KO mice, it is the lack of AG the major determinant factor of their overall better conditions and advocate for the design of analogs to UnAG rather than AG to therapeutically treat sarcopenia in humans.

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OC4.3

Clinical implications of Pan-genomic classification of pituitary neuroendocrine tumours

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Recently, we provided the first integrated genomic classification of pituitary neuroendocrine tumors (PitNETs), on a series of 134 tumors. This series covered all histological, secretion, invasion and growth speed types. This molecular classification supports the importance of pituitary lineage as proposed by the World Health Organization 2017 classification, but also individualizes new entities. Indeed, corticotroph tumors are split into three distinct molecular groups. In addition sparsely granulated somatotroph tumors cluster with thyrotroph and pluri-hormonal-PIT1 tumors. Finally, "null-cell" are gonadotroph tumors.
Aim
To explore the clinical implications of this new molecular classification;
Method
For the series of 134 tumors with genomic characterization (transcriptome, exome, miRnome, methylome, SNParray), extensive data were collected, including clinical (size, sphenoid and cavernous invasion), hormonal, pathological (WHO2017) and outcome (aggressiveness) features.
Results
-Immunohistochemistry thresholds:
Based on molecular classification, immunopositivity thresholds could be determined for prolactin, GH and ACTH in lacto-, somato- and corticotrophs.
-Aggressiveness:
On the whole cohort, aggressiveness did not appear as a major driver of genomic classification. The number of chromosomal alterations was not related to aggressiveness either, but rather to secretion type. Subgroup analyses revealed, for corticotrophs, an association between USP8 mutation status and aggressiveness. Indeed, USP8-mutated corticotrophs seemed less aggressive.
-Response to Temozolomide:
Temozolomide is currently recommended for treating aggressive tumors not responding to other treatments. Temozolomide is degraded by MGMT. The association between MGMT expression and response to temozolomide was evaluated in three patients. Expression level was high in one not responding, intermediate in one with partial response, and low in one with complete response. No negative correlation was found between MGMT expression and DNA methylation in MGMT locus on the whole cohort, including its promoter (median correlation coefficient 0.55; range: –0.27 to 0.76).
- Expression of somatostatin receptors:
Somatostatin receptor subtypes showed variable expression between molecular groups (Kruskal-Wallis test, $P<10–13$ and $P<10–15$ for SSTR2 and SSTR5, respectively). Notably, for corticotroph PitNETs, expression of SSTR5 was higher in USP8-mutated PitNETs compared with USP8-wild-type (Wilcoxon's $P<10–4$), supporting a potential value of USP8 mutation status for predicting response to pasireotide. Finally SSTR5 expression was also high in the group of thyrotroph tumors.
Conclusion
USP8-wildtype corticotroph adenomas with overt Cushing are more aggressive. MGMT promoter methylation is not correlated to MGMT expression. MGMT expression level may be associated to Temozolomide response.

mRNA expression level could be a predictor of temozolomide. SSTR5 expression is high in USP8-mutated corticotroph tumors.

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OC4.4

Thyrotropin/Thyrotropin receptor signaling deficiency impairs spatial learning and memory

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Purpose
Subclinical hyperthyroidism is associated with cognitive impairment, but the mechanism has remained unclear. As subclinical hyperthyroidism is characterized by significantly decreased thyrotropin (TSH) levels, this study aimed to investigate whether TSH regulates cognitive function.
Methods
The correlation between TSH and cognitive impairment was investigated in a cross-sectional population study including 382 participants with ages ranged from 21 to 82 years old. The role of TSH/TSH receptor (TSHR) signaling in spatial learning and memory was further examined by behavior tests in *Tshr*$^{-/-}$ mice. Dendritic spine, synaptic density and structure of hippocampal CA1 pyramidal neurons were detected by Golgi's method and electron microscopy. The mRNA and protein expression levels of learning and memory-related genes were assessed by RNA sequencing, real-time PCR, immunoblotting and immunofluorescence approaches.
Results
Serum TSH level correlated inversely with cognitive impairment in the current population. Consistently, *Tshr* deletion in mice led to significantly compromised performance in hippocampus-dependent tasks, reduced dendritic spine density and excitatory synaptic density as well as altered synaptic structure in CA1 subfield of the hippocampus. Furthermore, the mRNA levels of learning and memory-related genes were altered, and protein levels of CREB-regulated genes were downregulated in the hippocampus of *Tshr*$^{-/-}$ mice.
Conclusions
These findings reveal that TSH/TSHR signaling ablation impairs spatial learning and memory, indicating a decline in TSH level might contribute to the increased prevalence of cognitive impairment in subclinical hyperthyroidism patients.

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OC4.5

Durability of response and gender-based analysis from the LINC3 trial of osilodrostat in the treatment in cushing's disease

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Introduction
In a Phase II study, osilodrostat, a potent oral 11β-hydroxylase inhibitor, normalized mean urinary free cortisol (mUFC) in most patients with CD. We report the efficacy and safety of osilodrostat in a large CD patient population (NCT02180217).
Methods
In this study, open-label osilodrostat was initiated at 2 mg bid in 137 adults with CD and mUFC > 1.5×ULN, with dose adjustments every 2 weeks (range 1–30 mg bid) up to W12. At W26, patients achieving mUFC ≤ ULN at W24 without a dose increase after W12 ($n=71$) were randomized to continue osilodrostat ($n=36$) or matching placebo ($n=35$) for 8 weeks, followed by open-label osilodrostat until W48. Patients ineligible for randomization continued open-label osilodrostat ($n=47$). The primary endpoint was mUFC ≤ ULN at the end of the randomized withdrawal phase (W34) without a dose increase after W26.
Results
At baseline, median (range) mUFC was 3.5×ULN (0.3–69.6). At W34, significantly more patients in the osilodrostat group maintained mUFC ≤ ULN (without a dose increase after W26) than in the placebo group (86% vs 29%; OR 13.7, $P<0.001$). At W24, 53% of enrolled patients had mUFC ≤ ULN without a dose increase after W12. At W48, 66% of enrolled patients had mUFC ≤ ULN and 96% of enrolled patients had mUFC ≤ ULN at least once during the study, with a median time to first mUFC ≤ ULN of 41 days and no differences observed between males and females. In addition, 64/97 (66×0%) patients maintained normal mUFC for ≥6 months after the first mUFC normalization. By week 24, 72·2% were receiving an osilodrostat dose of ≤5 mg bid, irrespective of mUFC elevation at baseline. Median (range) duration of osilodrostat exposure was 75 weeks (1–165). By W48, 24 (18%) patients had discontinued the study, 15 (11%) because of adverse events (AEs). Overall, the most common AEs were nausea (42%), headache (34%), and fatigue (28%). AEs related to hypocortisolism and adrenal-hormone-precursor accumulation occurred in 51% and 42% of patients, respectively. No males experienced signs or symptoms related to increases in androgens or oestrogens. In females, AEs of hirsutism (8·8%), acne (8·8%), and hypertrichosis (0·7%) were reported, all grade 1–2, and none leading to study discontinuation.
Conclusion
Osilodrostat was significantly superior to placebo at maintaining mUFC ≤ ULN after randomized withdrawal, and normalized mUFC in two-thirds of enrolled patients at W48, with few patients discontinuing treatment because of AEs. This study demonstrates osilodrostat to be a highly effective treatment for CD, with good tolerability.

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OC4.6

Results from the phase 3, randomized, double-blind, placebo-controlled OPTIMAL study of oral octreotide capsules in adult patients with acromegaly

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Background
Many patients with acromegaly report limitations of long-acting somatostatin receptor ligand (SRL) injections, including ongoing disease symptoms near cycle-end and injection-site pain. Oral octreotide capsules (OOC) may provide an alternative to monthly injections. The phase 3 CHIASMA OPTIMAL study assessed efficacy and safety of OOC in patients with acromegaly controlled on injectable SRLs.
Methods
A multinational, randomized, placebo-controlled study was conducted in 56 patients ≥18 years of age with active acromegaly (IGF-I ≥1.3 ×ULN) and average IGF-I ≤ 1.0 ×ULN on stable dose of SRL injections (octreotide or lanreotide, ≥3 months). At baseline (1 month after last injection), patients were randomized to OOC or placebo (28/group) for 36 weeks, followed by an optional open-label extension (OLE). The primary endpoint was proportion of patients maintaining biochemical response, defined as IGF-I ≤ 1.0 ×ULN (2-value average at weeks 34 and 36). Secondary endpoints included need for rescue with injectable SRLs, GH response (GH < 2.5 ng/mL), and time to loss of IGF-I response (IGF-I > 1.0 and $1.3 ×ULN for 2 consecutive visits). Safety and tolerability were assessed.

Results
The primary endpoint was met, as 58% of patients receiving OOC maintained IGF-I response vs 19% receiving placebo ($P=0.008$). Mean IGF-I levels in patients receiving OOC were within the reference range at treatment end (0.97 × ULN) vs patients receiving placebo (1.69 × ULN). All secondary endpoints were met. Of patients receiving OOC, 75% completed 36 weeks without need for rescue therapy. However, 68% of the placebo group required rescue therapy. GH response was maintained at week 36 in a significantly larger proportion of patients receiving OOC than placebo (78% vs 30%; $P=0.001$). Median time to loss of IGF-I response was not reached by the end of the study for patients receiving OOC vs 16 weeks for the placebo group ($P<0.0001$). Five patients in the placebo group had IGF-I levels in the reference range at the end of 36 weeks. Only 2 (7% of placebo group) did not meet loss of response criteria anytime throughout the study. OOC were safe and well tolerated; no new/unexpected safety signals were observed. Most patients (55/56) experienced at least one treatment emergent adverse event; most were mild or moderate in intensity. Overall, 90% of patients who completed the trial on OOC opted to enter the open label extension phase.
Conclusion
These phase 3 data demonstrate OOC to be potentially safe and effective for treating adults with acromegaly.

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OC4.7

Fluid restriction results in a modest rise in plasma sodium concentration in chronic hyponatraemia due to SIAD; results of a prospective randomised controlled trial

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Fluid restriction (FR) is the recommended first-line treatment for chronic hyponatraemia due to syndrome of inappropriate antidiuresis (SIAD) in expert guidelines, despite the lack of prospective data to support its efficacy. We aimed to test the hypothesis that FR was more effective than no treatment. 46 patients with chronic SIAD were randomised to either fluid restriction (1 litre/day, FR) or no specific hyponatraemia treatment (NoTx) for one month. Inclusion criteria were euvolemia, plasma sodium (pNa) 120–130 mmol/l, urinary sodium (UNa) ≥30 mmol/l, urine osmolality (UOsm) $100 mOsm/kg and normal cortisol secretion. Patients with symptomatic hyponatraemia, alcohol dependence, diuretic therapy, and recent discontinuation of medications causing hyponatraemia, were excluded. The primary endpoints were change in pNa at day 4 and day 30, chosen to match the endpoints reported in the SALT trials. A rise in pNa of <5 mmol/l was defined as treatment failure. Data are expressed as median (IQR). The two groups were matched for age (74 yrs (68–80) in FR and 72 yrs (54–80) in NoTx, $P=0.55$), baseline pNa (127 (126–129) mmol/l FR and 128 (126–129) mmol/l NoTx, $P=0.36$) and urine osmolality (459 (345–604) mOsm/kg FR and 457 (287–556) mOsm/kg NoTx, $P=0.86$). Idiopathic SIAD accounted for 39% of FR, and 26% of NoTx, $P=0.15$. PNa rose by 3 (2–4) mmol/l by day 4 in FR ($n=23$), compared with 1 (0–3) mmol/l NoTx ($n=23$), $P=0.005$. There was minimal additional rise in pNa by day 30; pNa increased from baseline by 4 (2–6) mmol/l in FR ($n=17$), compared with 1 (0–1) mmol/l NoTx ($n=15$), $P=0.04$. By day 4, 17% of FR had a rise in pNa of ≥5 mmol/l, compared with only 4% NoTx, $P=0.35$. By day 30, 47% of FR had a rise in pNa of $5 mmol/l, compared with only 6.7% NoTx, RR 7.1, $P=0.02$. There was no statistically significant difference in the proportion of patients reaching pNa $130 mmol/l by day 4, 61% FR compared with 39% NoTx, $P=0.24$, or by day 30, 71% FR and 40% NoTx, $P=0.15$. FR results in a modest rise in pNa after three days in patients with chronic SIAD, with minimal additional rise thereafter. Less than half of patients achieve a target rise in pNa ≥5 mmol/l after 30 days of FR, emphasising the clinical need for additional therapies for SIAD.

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Thyroid

OC5.1

TSH-Independent upregulation of thyroid-specific gene expression in dehal1 knockout mice

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Background
Most thyroid specific genes are transcriptionally regulated by TSH-TSHR signalling and T4-driven negative feedback of TSH secretion at the pituitary. However, local autoregulation of transcription has been described from IGF-IGFR, follicular thyroglobulin, or iodine. We aimed to investigate the TSH dependency of thyroid transcriptional regulation in the *Dehal1* knockout, devoid of iodide-recycling capacity from iodotyrosines.
Methods
Dehal1 knockout (KO) and wild-type (WT) mice were fed with a diet containing high iodine (5.6 µg/l/day, to secure iodine sufficiency) for 28 days. Plasma TSH and T4 were determined on days 0 and 28 by radioimmunoassay and LC/MS-MS, respectively. After sacrifice, RNA from thyroids were isolated and cDNA-qPCR were used to determine expression levels of genes involved in basal/apical iodide transport (*Slc5a5*, *Slc26a4*, *Slc26a7*), nuclear transcription (*Pax8*, *Nkx2-1*, *Foxe1, Glis3*) and thyroid hormone synthesis and secretion (*Tshr*, *Tg*, *Tpo*, *Duox2*, *Duox2*, *Dehal1*, *Slc16a2, Dio1*).
Results
Under sufficient iodine, TSH was equal in both genotypes (logTSH: 1.45±0.1 vs 1.45±0.4 mU/l, $P>0.05$). Plasma T4 (58.5 vs 59.9 ng/ml) and T3 (0.5 vs 0.47 ng/ml) were normal in both genotypes respectively ($P>0.05$). However, despite complete euthyroidism, *Dehal1*-KO mice showed a dramatic increase of overall gene expression at baseline, as compared to WT mice (mean 8.7-fold upregulation, 14 genes studied) including hormone-synthetic *Tshr* (8.7-fold), *Tg* (10.2), *Tpo* (5.8), *Duox2* (8.4), *Duoxa2* (4.5), *Slc16a2* (8.2) and transcriptional factors *Nkx2-1* (6.4), *Pax8* (28), *Foxe1* (7.5) and *Glis3* (11). Interestingly, basal and apical iodide transporters showed opposite modulation: *Slc5a5 (Nis)* was maximally overexpressed in KO mice (20-fold) while expression of apical *Slc26a4* and *Slc26a7,* exceptionally, remained unchanged.
Conclusion
A TSH-independent mechanism of transcriptional regulation is active in the thyroid glands of *Dehal1* knockout mice, which are fully euthyroid. This mechanism is not indiscriminate but gene-specific, since apical iodide transporters pendrin and Slc26a7 are preserved from regulation. Our data suggest that intrathyroidal, yet unspecified signals, may regulate specific gene expression to compensate for the deficient iodide recycling before hypothyroidism occurs.

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OC5.2

Overtreatment of papillary thyroid microcarcinoma: a snapshot from the italian thyroid cancer observatory

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Background and Aim
The incidence of papillary thyroid microcarcinoma (mPTC) has dramatically increased in the last decades. The majority of these tumors remain small and clinically silent, only small number progress. Clinical practice guidelines currently suggest avoiding the cytological examination of subcentimeter nodules and reducing surgeries for mPTC. Several risk factors have been identified as strongly associated with a high-risk phenotype for mPTCs (e.g. gross nodal metastasis, extranodal extension). This study aims to evaluate the prevalence, the risk of recurrence and the management of mPTCs in different Italian thyroid clinical centers.
Methods
The Italian Thyroid Cancer Observatory (ITCO) was established in 2013 to collect prospective data on thyroid cancers consecutively diagnosed in member centers. We collected data of all histologically confirmed mPTCs present in the database at the end of December 2019. The risk stratification

was classified according to the 2015 ATA guidelines after surgery and it was re-classified after radioiodine treatment.
Results
A total of 7747 patients, enrolled by 48 centers were included in the initial cohort. Overall, 3172 cases were mPTCs (40.9%). No significant difference in the prevalence of mPTC was detected over time. The initial risk stratification (after surgery) included: 2115 (66.7%) low-risk PTCs, 989 (31.2%) intermediate-risk mPTCs and 68 (2.1%) high-risk mPTCs. 991 patients (31.2%) underwent radioiodine treatment. Among these, the initial (after surgery) risk stratification was as follows: 385 (38.8%) low-risk PTCs, 550 (55.5%) intermediate-risk mPTCs and 56 (5.7%) high-risk mPTCs. After radioiodine treatment, the risk stratification was re-classified as follows: 360 (36.3%) low-risk PTCs, 522 (52.7%) intermediate-risk mPTCs and 109 (11%) high-risk mPTCs.
Conclusions
Despite the efforts to reduce the number of surgeries for mPTCs, these interventions are still very common. The optimal management of low-risk microPTC represents a major clinical issue. Furthermore, in recent years, in spite of the updated guidelines and scientific literature data, no relevant differences were measured in real-world clinical practice in Italy. In this large and contemporary cohort of patients, radioiodine treatment allows us to re-classify risk stratification for about 5% of mPTC patients.

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OC5.3

Acute pancreatitis associated with methimazole treatment: A retrospective analysis of administrative health databases conducted in the Piedmont Region, Italy

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Purpose
Methimazole (MMI) is a widely used antithyroid agent for first-line treatment of hyperthyroidism. A warning has been recently issued by the European Medicine Agency (EMA) regarding a potential increased risk of acute pancreatitis (AP) in MMI users, based on evidences from published case reports and post-marketing surveillance. The aim of this study was to investigate the association between MMI treatment and the diagnosis of AP in drug users.
Materials and methods
Retrospective analysis of administrative databases: inhabitants registry, hospital discharge records (HDRs) and the drug claims registry of the Piedmont Region, Italy. In the study period 2013–2018, MMI users were identified using the drug claims registry (ATC H03BB02) and cases of AP through HDRs (ICD-9-CM 577.0). General population (non-users) was used as comparative group. To investigate the association between MMI treatment and AP risk, we identified hospitalizations for AP occurring in each trimester comprised in the first 18 months following the first prescription of MMI. Poisson regression was used to estimate the age- and sex-adjusted ***Rate Ratios*** (adjRRs), and the relative 95% confidence intervals (CI), comparing rates of AP between MMI users and non-users. The absolute risk of AP in MMI users was also calculated.
Results
A total of 23,087 users of MMI were identified. Among these, 13 hospitalizations for AP were recorded within the first trimester of treatment, for a total of 61 hospitalizations occurring within the first 18 months. The crude RR for AP in the first trimester of treatment was 270 per 100,000 person-year [95% CI 170–428] in MMI users and 60 per 100,000 person-year [95% CI 59–61] in the general population. Values of adjRRs according to trimesters of observation were 3.40 [95% IC 2.12–5.48] for the first, 2.40 [95% IC 1.36–4.23] for the second, 2.80 [95% IC 1.66–4.73] for the third, 1.20 [95% IC 0.54–2.68] for the forth, 1.60 [95% IC 0.80–3.21] for the fifth and 0.80 [95% IC 0.30–2.14] for the sixth trimester. The absolute risk for AP in MMI users was less than 0.39%, considering both sex and different ages.
Conclusions
AP should be considered as a rare-uncommon adverse drug reaction in MMI-users; further studies are warranted to identify subgroups at higher risk.

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OC5.4

Drug repurposing identifies inhibitors of the proteostasis network to augment radioiodine uptake in combinatorial approaches targeting thyroid cancer

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New combinatorial drug strategies are urgently needed to improve radioiodine (RAI) uptake and efficiently ablate thyroid cancer cells, thereby reducing the risk of recurrent disease. Drug repurposing offers the promise of identifying already approved compounds capable of inducing sodium iodide symporter (NIS) function to enhance iodide uptake. However, a lack of thyroid cell-based assays amenable to high-throughput screening has limited progress. We utilised the mutated yellow fluorescent protein (YFP) as a surrogate biosensor of intracellular iodide and screened the Prestwick Chemical Library (1200 drugs; 95% approved) for quenching of YFP fluorescence. This allowed us to identify putative candidate drugs which increased iodide uptake >2 SD above mean. Categorisation of these revealed a high proportion of drugs that modulate the proteostasis network (19/48; ~40%), including key processes in protein homeostasis such as endoplasmic reticulum-associated protein degradation (ERAD) and autophagy. Secondary screening validated the activity of proteostasis modulators in enhancing iodide uptake after ranking 73 leading compounds based on their pharmacologic (AUC, E_{MAX} and EC_{50}) and specificity of response (NIS+ve vs NIS-ve YFP-thyroid cells) at ten different drug doses (0.1 to 50 μM). Of importance, several repurposed drugs (e.g. ebastine, Prestwick N, Prestwick C and clotrimazole) in combination with the HDAC inhibitor vorinostat induced a robust enhancement in RAI uptake in thyroid cancer cells (TPC-1 and 8505C NIS+ve cells, up to 11-fold vs DMSO, $P<0.001$), which was significantly greater than using vorinostat alone (up to threefold, $P<0.01$). For clotrimazole, we designed 7 new chemical derivatives, 3 of which showed enhanced aqueous solubility and retained the ability to significantly enhance RAI uptake. TaqMan RT-PCR revealed that, in contrast to vorinostat, our repurposed drugs failed to alter NIS mRNA expression, highlighting post-transcriptional mechanisms. Critically, 11 repurposed drugs induced significant gains in RAI uptake in human primary thyroid cells (up to 4.1-fold; $P<0.05$), the most physiological setting for NIS function. In conclusion, we performed high-throughput screening and identified proteostasis modulators, as well as other repurposed drugs, that markedly enhance radioiodine uptake. Further clinical investigation of these drugs might offer new combinatorial approaches, especially with existing therapies, to improve the treatment of thyroid cancer.

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OC5.5

Thyroid dysfunction induced by immune checkpoint inhibitors is associated with a better progression-free-survival and overall survival in non-small cell lung cancer: an original cohort study

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Objective
Immune checkpoint inhibitors (ICI) are used for treatment of non-small cell lung cancer (NSCLC) and are associated with immune-related adverse events (irAEs), especially thyroid dysfunction. Few studies found an association between thyroid dysfunction and response to Nivolumab in the NSCLC The objective of this retrospective cohort study was to investigate the association between the occurrence of thyroid dysfunction in patients treated with Nivolumab for a NSCLC and treatment efficacy and to assess whether this association is function of severity and type of thyroid dysfunction.
Materials and methods
This study was performed at a referral oncology center between July 20, 2015 to June 30, 2018. Inclusion criteria were patients with histologically

confirmed stage IIIB/IV NSCLC and progressive disease who initiated anti-PD-1 blockade (Nivolumab). The exclusion criteria were: patients whose primary tumor was not from bronchopulmonary origin; patients with a history of thyroid disease; patients not having any thyroid monitoring before/ during Nivolumab treatment. Thyroid function (TSH ± fT4, fT3) was monitored and patients were classified according to thyroid dysfunction occurrence (TD(+) vs TD(−)) and according to severity (moderate thyroid dysfunction: TSH level between 0.1–0.4 or 4.0–10 mIU/l, and severe thyroid dysfunction: TSH ≤ 0.1 or ≥10 mUI/l) and subtypes (isolated hypothyroidism, isolated thyrotoxicosis or thyroiditis (thyrotoxicosis then hypothyroidism)). The primary clinical endpoints were the overall survival (OS) and progression-free survival (PFS). The secondary clinical endpoints were the objective response rate (ORR), the disease control rate (DCR) and the duration of response.
Results
Among 194 eligible patients, 134 patients (median age, 63 yo; 70.1% male) were included. Forty (29.9%) patients were classified in TD (+) and had a longer OS of 29.8 months (15.2-not reached) vs 8.1 months (3–20.4) in TD (−) group ($P<0.001$). PFS was also longer (8.7 months (2–27.1) in TD (+) vs 1.7 months (1.6–3.6) in TD (−) group ($P<0.001$). Treatment response was also higher in TD(+) group vs TD(−) group : ORR was of 47.5% vs 12.8% ($P<0.001$), PRR was of 20% vs 7.4% ($P=0.04$), DCR was of 70% vs 27.7% ($P<0.001$). In Cox proportional hazards analysis, thyroid dysfunction remained an independent prognostic factor associated with OS/PFS. Severity and subtypes of thyroid dysfunction were not correlated with survival outcomes.
Conclusions
This study found a high prevalence of thyroid dysfunction under Nivolumab, which appears to be an independant prognostic factor regardless of thyroid dysfunction severity and subtypes.

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OC5.6

Patients with APECED have increased early mortality due to endocrine causes, malignancies and infections

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Context
Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) is an autoimmune endocrinopathy with severe and unpredictable course. Previous studies have reported increased mortality in patients with APECED. However, the impact of APECED on mortality has not been previously determined.
Objective
To systematically study overall and cause-specific mortality in patients with APECED. Design and Setting: A follow-up study of Finnish patients with APECED in 1971–2018. The clinical picture of the disease was studied from the patient records. Causes and dates of death were collected from Finnish registries using the Finnish personal identity codes as patient identifiers. Overall and cause-specific standardized mortality ratios (SMRs) were determined by comparing the observed numbers of death and those expected on the basis of respective population death rates in Finland.
Patients
Cohort of 91 Finnish patients with APECED. Main outcome measure SMR.
Results
Of all patients 29 (32%) had deceased during the follow-up period. The overall disease mortality was significantly increased [SMR 11; 95% confidence interval (CI) 7.2–16; $P<0.001$]. Altogether 21 patients (72%) had deceased before 45 years of age. The relative risk (SMR) was highest in the youngest age groups but the absolute excess risk was similar (about 10 per 10,000 person-years) in all age categories. The highest SMRs were seen for endocrine and metabolic diseases (SMR 570; 95% CI 270–1000; $P<0.001$) and for oral and esophageal malignancies (SMR 170; 95% CI 68–360; $P<0.001$). Mortality was also increased for infections, diseases of digestive system, alcohol-related deaths, and for accidents. No significant differences in SMR were found between subgroups of patients divided according to number of clinical manifestations or patients with or without hypoparathyroidism or adrenal insufficiency in the beginning of follow-up.
Conclusions
Patients with APECED have significantly increased mortality already at an early age and mortality is similarly increased in all age groups. Highest SMRs are found in causes that are directly related to APECED. In addition, our results suggest increased mortality due to previously unreported causes, such as infections. Increased alcohol- and accident-related deaths may be influenced by psychosocial factors.

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OC5.7

Triiodothyronine (T3) use in hypothyroidism and effects on cancer and mortality

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Background
The prescription of triiodothyronine (T3) for hypothyroidism is increasing worldwide, however, long-term effects of its use are largely unknown. Previous studies have suggested possible association between T3 use and breast cancer. The aim of the study was to examine the effects of T3 use on cancer incidence and mortality.
Material
Our sample included the full adult population of individuals living in Sweden with at least three purchases of thyroid replacement hormones between July 2005 and December 2017. Individual-level data on drug purchases were linked to register data on cancer incidence and mortality. There were 575,461 individuals with at least three purchases of thyroid replacement hormones, of which 11,147 had at least three purchases of T3 including combinations of l-thyroxine (T4) and T3. Individuals were followed for 7.4 years on average.
Methods
We applied Cox-regression with a time-varying exposure variable, comparing "T3 users" (individuals with at least 3 cumulative purchases of T3) with "T4 users" (the rest). Outcomes included breast cancer incidence, any cancer incidence, all-cause mortality, any cancer mortality, and breast cancer mortality. We adjusted for age, gender, previous thyroid cancer, previous other cancer, use of antithyroid preparations, use of sex hormones, and dosage in multivariate analyses.
Results
Multivariate analyses comparing T3 and T4 users produced a hazard ratio of 1.03 (95% CI 0.83–1.29) for breast cancer incidence (only women), 0.96 (0.85–1.07) for any cancer incidence, 0.92 (0.81–1.05) for all-cause mortality, 0.85 (0.66–1.10) for any cancer mortality, and 1.23 (0.69–2.22) for breast cancer mortality (only women), none of which was significant. Analyses focusing only on new thyroid replacement users (after July 2006) and analyses stratified by sex yielded similar results, with insignificant estimates that were close to one.
Conclusion
In this large Swedish long-term register-based study, the use of T3 compared to T4 did not lead to increased breast cancer incidence, any cancer incidence, all-cause mortality, any cancer mortality, and breast cancer mortality. Other possible negative effects of T3 use were not analyzed in this study and cannot be excluded.

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Hot Topics (Including Covid-19)

OC6.1

Effects of nonpeptide orally bioavailable ACTH antagonists on adrenal gland size and function in rats

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Cushing's disease (CD) and Ectopic ACTH syndrome (EAS) stem from excess circulating adrenocorticotropic hormone (ACTH) and resulting hypercortisolemia. In CD, excess ACTH is secreted from pituitary tumors, whereas excess ACTH in EAS arises from nonpituitary tumors. ACTH acts on the adrenal melanocortin type 2 (MC2) receptor to control the synthesis and secretion of adrenal hormones, including the stress hormone cortisol (corticosterone in rats) which accounts for the comorbidities of CD and EAS. Availability of a potent ACTH antagonist that can normalize cortisol in patients with diseases of excess ACTH will be a major advance in endocrinology. Additionally, an ACTH antagonist will have utility in congenital adrenal hyperplasia (CAH) because of its ability to block production of excess adrenal androgens. Crinetics is evaluating and developing ACTH antagonists for the treatment of diseases of excess ACTH. To our knowledge, these compounds represent the first potent nonpeptide ACTH antagonists to demonstrate *in vitro* potency and *in vivo* efficacy. As a result, the direct effects of sustained MC2 receptor blockade on the structure and function of the adrenal gland have never been able to be assessed. We examined the effects of several orally bioavailable ACTH antagonists across a range of doses on Sprague-Dawley rat adrenal gland weight, histology, and hormone levels in repeat dosing (7–14 days) studies. Sustained MC2 receptor antagonism dose dependently blocked activity of ACTH at the level of the adrenal gland and reduced plasma corticosterone levels. In the normal rat, this resulted in dose-dependent atrophy of the adrenal gland as assessed by organ weights and microscopically. The atrophy was primarily observed in the cortisol producing zona fasciculata, as well as in the zona reticularis, with smaller reductions noted in the aldosterone producing zona glomerulosa. Additionally, hypertrophy of the adrenal glands caused by continuous subcutaneous administration of exogenous ACTH was reversed by treatment with an ACTH antagonist. The adrenal effects were accompanied by expected changes in corticosterone levels. These preclinical findings demonstrate the therapeutic potential of ACTH antagonism and provide a strong rationale for development of an orally bioavailable drug that can be used to combat CD, EAS, and CAH.

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OC6.2

Experimental induced autoimmune thyroiditis in wistar rats: possible protective role of selenium

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Experimental autoimmune thyroiditis (EAT) has been used to simulate human autoimmune thyroid disease for decades. EAT can be easily induced in genetically susceptible strains of mice by excess iodine ingestion or by immunization with mouse thyroglobulin. Excess iodine may induce and exacerbate autoimmune thyroiditis (AIT) in humans and animal models. In order to assess the potential protective mechanisms of selenium (Se) in thyroid autoimmunity, we evaluated the effects of inorganic Se (sodium-selenite) administration on thyroid morphology and follicular cytology in adult Wistar rats with iodine-induced AIT. Forty-eight adult Wistar rats (24 females, 24 males) were allocated to one of four dietary regimens: C0: control; C1: only potassium-iodine (KI); C2: concomitant KI and Se; C3: only KI initially, followed by Se administration. For AIT induction, the rats were fed with 0.05% KI for 56 days. Se-treated rats received 0.3 mg/l sodium-selenite in drinking water. Thyroid tissue for pathologic diagnosis was collected after 7 days in C0, 56 days for C1 and C2, and 112 days in C3. In C1, moderate to severe thyroiditis was observed in 83% males and 50% of female rats ($P=0.223$). In C3 only, 16.7% of male rats developed mild thyroiditis and none in C2, while no females were identified with moderate to severe thyroiditis in both C2 and C3. The male rat thyroid morphology showed that the C1 group had higher mean values of thyroid follicles compared to C0, the control group (73.82 μm vs 50.13 μm, ×100), and to the C2 (73.82 μm vs 53.74 μm,×100). In female rats, the highest mean value of thyroid follicles was recorded in C1 group (57.56 μm,×100), and the lowest in C2 (47.32 μm, ×100). Thus, the administration of Se was proved to have protective effects against thyroiditis cytology in both male and female Wistar rats.

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OC6.3

Expression of estrogen-related receptors and epidermal growth factor receptor in normal adrenal cortex and adrenocortical tumors: A possible role of GPR30 and EGFR in adrenocortical malignancy

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Introduction
The majority of adrenal neoplasms are benign while adrenocortical carcinomas (ACC) are rare with poor prognosis. Previous studies indicated that estrogens play important role in the etiology and progression of adrenocortical tumors. Estrogens exert genomic activities trough the estrogen-receptor (ER) subtypes α and β, while the non-genomic effects are mediated by membrane-bound-G-protein-coupled-ER-30 (GPR30). Although estrogens induce cancer cell proliferation through ERα, ERβ appears to exert a protective effect. In vitro experiments showed that treatment with ERα antagonist as well as GPR30 agonist reduces proliferation in H295R cells. However, data on the expression profile of ERs in normal and human adrenocortical neoplasms are limited. Epidermal growth factor receptor (EGFR) found to be highly expressed in ACC. The expression of EGFR has been negatively correlated with expression of ER in other cancers, while data regarding the correlation between ERs and EGFR expression in adrenocortical neoplasms are missing.
Aim
We aimed to investigate the expression profile of ERs and EGFR in adrenocortical neoplasms and correlate it with their biological behavior.
Material and methods
Total RNA was extracted from fresh frozen tissue of: eight non functional adenomas (NFA), eight cortisol producing adenomas (CPA), their adjacent normal adrenal tissues (NAC) AND eight adrenocortical carcinoma (ACC). The expression of ERα, ERβ, GPR30 and EGFR genes was evaluated by qPCR. The Immunohistochemistry (IHC) was performed to evaluate the EGFR and GPR30 protein levels.
Results
The expression of both ERα and GPR30 were higher in the CPA as compared to their adjacent normal tissue ($P<0.05$) while there was no significant difference in ERβ and EGFR mRNA levels between CPA, NFA and their adjacent normal tissues. The expression of GPR30 was significantly higher in ACC compared to either NFA or NAC groups ($P<0.05$), and marginally higher in ACC compared to CPA. The expression of ERα and EGFR was higher in ACC compared to either CPA or NFA ($P<0.1$). IHC confirmed the higher expression EGFR in ACC compared to the adrenal benign tumors. A marginal positive correlation between EGFR and GPR30 expression was observed in ACC.
Conclusion
To our knowledge this the first study to evaluate the expression of membrane-bound GPR30 in human adrenocortical neoplasms. Our preliminary data suggest a possible role of GPR30 and EGFR in adrenocortical malignancy, while ERα may play a role in functional adenomas. Further studies with larger number of samples are required to elucidate the role of ERs and EGFR on the adrenal tumorigenesis.

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OC6.4

High-dose Vitamin D supplementation reduces inflammation and improves microcirculation in patients with diabetic peripheral neuropathy – a randomized control trial

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Background
In recent years, the role of vitamin D in improving the profile of inflammatory markers in order to prevent and treat diabetic neuropathy and microcirculation disorders has been actively studied.
Aims
The research goal was to study the dynamics of inflammatory markers, clinical manifestations of diabetic peripheral neuropathy and laser Doppler flowmetry of skin microcirculation during treatment with various doses of cholecalciferol in patients with type 2 diabetes and DPN.
Materials and methods
A single-center, open, randomized trial included patients with type 2 diabetes with DPN. Sixty-seven patients were randomized into 2 groups, where Group I took cholecalciferol in a dose of 5,000 IU/week for 24 weeks, and Group II took a dose of 40,000 IU/week. At the start and the end of the trial, the body mass index (BMI), glycated hemoglobin level (HbA1c), 25(OH)D, PTH, interleukins-1β, −6, −10 (IL), C-reactive protein (CRP), and tumor necrosis factor α (TNFα) levels were determined; the survey was conducted on the NSS, NDS and visual analog scales. Using laser Doppler flowmetry, one compared the initial and final indicators of the baseline blood flow and microcirculation (MC) against functional samples (postural and occlusal). Control measurements of LDF parameters were performed on 16 subjects without diabetes mellitus (eight men/eight women, 51.8±3.7 years).
Results
Sixty-two patients completed the study. Group I ($n=31$, W16) and Group II ($n=31$, W15) were initially comparable by age, gender, BMI, HbA1c level, NSS, NDS, and VAS. Initially, LDF indicators were significantly lower compared to the group without T2DM. Vitamin D deficiency was detected in 78% of patients with T2DM. After 24 weeks of taking cholecalciferol in Group II, there was a significant decrease in BMI, in the levels of HbA1c and IL-6, and an increase in the level of IL-10, as well as the improvement of cutaneous MC and functional test parameters, while in Group I these changes were not detected. A correlation was established between the final level 25(OH)D and IL-6 ($r=-0.378$, $P=0.036$), IL-10 ($r=0.483$, $P=0.006$), BMI ($r=-0.388$, $P=0.031$) and HbA1c ($r=-0.388$, $P=0.031$).
Conclusion
Receiving cholecalciferol in a dose of 40,000 IU/week over the course of 24 weeks is associated with a decrease in BMI, an improvement in glycemic control and the profile of pro-inflammatory markers, a decrease in the severity of diabetic peripheral neuropathy, and an improvement in the LDF parameters of cutaneous MC and functional tests in patients with type 2 diabetes and DPN

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OC6.5

TransCon PTH, a long-acting PTH, in patients with hypoparathyroidism: Results of the phase 2 PaTH forward trial

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Background
Hypoparathyroidism (HP) is characterized by low serum calcium (sCa) and high serum phosphate (sP). Standard of care (SoC), active vitamin D and calcium, raises sCa and sP and increases burden of illness on HP patients by worsening hypercalciuria and the CaxP product. Parathyroid hormone (PTH)(1–84)($t_{1/2}$ ~2–3 hrs) is approved and can raise sCa and allow partial withdrawal of SoC, but does not sufficiently control urine calcium or symptomatic hypo- or hypercalcemia. [NATPARA Package Insert; Khurana M *et al*. 2019] TransCon PTH, an investigational prodrug of PTH(1–34) transiently bound to an inert carrier via a linker, is under development for the treatment of HP. Linker auto-cleavage occurs under physiologic conditions, releasing active PTH at a controlled rate with a $t_{1/2}$ ~60 hrs.
Methods
PaTH Forward is a phase 2, double-blind, placebo-controlled trial evaluating TransCon PTH in adult HP patients treated with SoC. Subjects received fixed-dose TransCon PTH 15, 18, or 21 μg/day or placebo for 4 weeks, followed by an open-label extension period during which subjects could titrate their individual TransCon PTH dose (6–30 μg/day). The primary composite endpoint at Week 4 required 1) normal sCa, 2) normal (or ≥50% decrease from baseline) fractional excretion of calcium (FECa), 3) not taking active vitamin D, and 4) taking ≤1000 mg/day of calcium.
Results
At Week 4, significantly more subjects (50%) on TransCon PTH achieved the primary endpoint vs (15%) subjects on placebo (Table). sP decreased from baseline by 20% in subjects on TransCon PTH vs 1% on placebo. Increase from baseline in subjects meeting FECa endpoint was 42% on TransCon PTH vs 0% on placebo. Free PTH showed stable levels in the lower half of the normal range at both 2 and 4 weeks. TransCon PTH was well-tolerated; no subjects discontinued treatment or withdrew from the trial during the 4-week period, and no SAEs or severe AEs were reported. No subjects on TransCon PTH showed symptomatic hypocalcemia vs 7% on placebo.
Conclusions
Results from the initial 4 weeks of the PaTH Forward Trial demonstrated the TransCon PTH met the primary endpoint without increased incidence of symptomatic hypocalcemia despite a fixed dose. This trial will help inform the starting dose and SoC titration schedule for the phase 3 trial.

Week 4

	TransCon PTH ($n=44$)	Placebo ($n=13$)	*P*-value
Off active vitamin D and ≤ 500 mg/day calcium	82%	15%	$P<0.0001$
Off active vitamin D and calcium	50%	0%	$P=0.0008$
Primary Endpoint	50%	15%	$P=0.0305$

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OC6.6

Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalised with COVID-19 are associated with greater disease severity

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Background
The pandemic of Coronavirus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is associated with higher fatality in respect of male sex, advancing age, obesity, diabetes, hypertension, climatic factors and, in the UK and North America, with darker-skinned ethnicities; in all of which circumstances vitamin D deficiency (VDD) is more common. 25(OH)D levels reach their nadir at the end of winter and have been associated with increased risk of acute respiratory tract infections, which is mitigated by vitamin D supplementation. As seasonal VDD is highly prevalent in North-East England, physicians in Newcastle-upon-Tyne Hospitals (NuTH), a large tertiary NHS centre, decided to measure admission serum 25(OH)D levels in patients with COVID-19, to inform a treatment protocol adjusted according to the severity of baseline deficiency.
Objectives
To evaluate implementation of a local protocol for treatment of VDD among inpatients with COVID-19; to assess the prevalence of VDD, and examine potential associations with disease severity and fatality.
Methods
We performed a retrospective interim audit of a local care pathway for hospitalized patients with COVID-19-related illness. 134 patients with documented COVID-19 infection were included. We determined the prevalence of VDD, implementation of the local treatment protocol and relationship of baseline serum 25(OH)D with markers of COVID-19 severity and inpatient fatality vs recovery.
Results
55.8% of eligible patients received Colecalciferol replacement, albeit not always loaded as rapidly as our protocol suggested. No cases of new hypercalcaemia occurred following treatment. Patients admitted to ITU were younger than those managed on medical wards (61.1 years ± 11.8 vs 76.4 years ± 14.9, $P < 0.001$), with greater prevalence of hypertension, higher baseline respiratory rate, National Early Warning Score-2 and C-reactive protein level. While mean serum 25(OH)D levels were comparable [ITU: 33.3 nmol/l, 95% Confidence Interval (CI) 28.0–38.5 nmol/l vs Non-ITU: 48.2 nmol/l, 95% CI 40.3–56.0 nmol/l, $P = 0.2$) only 19% of ITU patients had 25(OH)D levels greater than 50 nmol/l vs 39.1% of non-ITU patients ($P = 0.02$). However, there was no association with fatality, potentially due to small sample size and prompt diagnosis and treatment of VDD.
Conclusions
Patients requiring ITU admission were more frequently vitamin D deficient than patients on medical wards, despite being significantly younger. These data suggest an important association between VDD and COVID-19 severity. Larger prospective studies and/or clinical trials are urgently needed to elucidate the role of vitamin D as a preventive and/or therapeutic strategy for mitigating the effects of COVID-19 infection.

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OC6.7

Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19

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Coronavirus disease 2019 (COVID-19), may lead to a severe acute respiratory syndrome requiring hospitalization and assisted ventilation with high lethality. Replication of SARS-CoV, MERS-CoV and Ebolavirus is calcium-dependent and hypocalcemia has been frequently reported in all these infections. Despite already many studies reporting on clinical and laboratory presentation of COVID-19 patients, including inflammatory and organ injury biomarkers, only one case report has so far described hypocalcemia in COVID-19. The aim of our study was to investigate the incidence of hypocalcemia in a large single center population of COVID-19 patients and evaluate its clinical implications. We retrospectively included 531 COVID-19 patients (aged ≥ 18 years) with serum ionized calcium (Ca^{2+}) evaluation from arterial blood gas test (ABG) performed at initial evaluation in our Emergency Departments (ED). We collected two different Ca^{2+} levels, a real level (“actual calcium (AC)”) and a corrected for a pH 7.4 (“standardized calcium (SC)”). Hypocalcemia was defined as a calcium levels below 1.18 mmol/l. We excluded patients with comorbidities and concomitant therapies influencing calcium metabolism. Hypocalcemia was found in 462 patients (82%) with AC levels and in 414 (78.6%) patients with SC levels. Severe hypocalcemia (below 0.99 mmol/l) was found in 18 (AC, 3.4%) and 10 (SC, 1.9%) patients. Hypocalcemic patients were more frequently males (AC, 69% vs 57% $P = 0.06$; SC, 70% vs 60% $P = 0.046$) and older (AC, 59 yr [51–69] vs 53 [45-67] $P = 0.01$). LDH and PCR levels were very significantly higher in hypocalcemic vs normocalcemic patients (AC, LDH: 372 U/l [287–466] vs 271.5 [202.25–347.5] $P < 0.001$; PCR: 71.55 mg/dl [31.22–132.4] vs 24 [4.65–77.65] $P < 0.001$; SC, LDH 70.25 mg/dl [30.87–130.35] vs 38 [11.2–105.9] $P < 0.001$; PCR 377 U/l [289–467] vs 307 [236–399] $P < 0.001$). In univariate and multivariate analyses hypocalcemia was an independent risk factor associated with hospitalization. Fifty-eight patients died (11.5%) and 62 (11.7%) were admitted in ICU. Hypocalcemia at admission was significantly associated to these two outcomes only in univariate but not in multivariate analyses. To our knowledge this is the first study that reports very high incidence of hypocalcemia in a large monocentric population of COVID-19 patients at initial hospital evaluation. Since hypocalcemia is highly incident in COVID-19 patients, predicts the need for hospitalization and may be life threatening if severe potentially worsening the COVID-19 morbidity at the cardiovascular level we suggest that ionized calcium should always be assessed at initial hospital evaluation, monitored and eventually adequately treated in all COVID-19 patients.

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Endocrine-related Cancer

OC7.1

Is Carney complex a breast cancer predisposing syndrome? prospective study of 50 women

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Introduction
Carney Complex (CNC) is a rare genetic syndrome, with multiple endocrine and non-endocrine neoplasia, mostly due to inactivating mutations of the *PRKAR1A* gene. CNC has a wide spectrum of manifestations : most frequently skin lesions, cardiac myxomas and primary pigmented nodular adrenocortical dysplasia (PPNAD), but also thyroid nodules, schwannomas, breast tumors (mainly myxoid fibroadenomas and ductal adenomas)… The present study was designed to describe the characteristics of breast lesions diagnosed in CNC patients and their association with other manifestations of CNC and *PRKAR1A* genotype. Since breast cancer is the most frequent cancer in women and the leading cause of death from cancer worldwide, malignant breast lesions were carefully analysed.
Methods
This cohort comes from a 3 years follow-up multicenter French prospective study of 70 CNC patients (Espiard, *et al*., JCEM 2020). The 50 included women here were analyzed for CNC manifestations and particularly breast lesions, with systematic mammography, genotype and hormonal settings, in order to characterize breast lesions, look for association with other CNC manifestations and assess the frequency and average age of breast cancer in this population.

Results
Among the 38 women with breast imaging, 14 (28%) had breast lesions, half of them bilateral. Ten women (20%) presented with benign lesions: fibroadenomas (70%), bilateral polyfibromatosis (30%), diffuse myxomatosis (20%)… Six women had breast carcinomas (12%) : five had invasive cancer before 50 years old (10%) and one had ductal carcinoma *in situ* at 54 years old. One patient presented with recurrent contralateral breast cancer. The average age of breast cancer was 44.7 years old, 17 years younger than in the general population, and relative risk of breast cancer in women less than 50 years old was threefold higher in CNC patients compared to general population. Breast cancer had good prognosis factors: all lesions were N0M0, hormonal receptor positive, HER negative, except for one at metastatic stage at diagnosis. All the participants were alive at the end of the study, the observation period ranging from 7 to 14 years. All Breast carcinomas occurred in *PRKAR1A* mutated patients. The occurrence of carcinomas was associated neither with conventional risk factors for breast cancer, nor with any other CNC manifestations.
Conclusion
Breast lesions are frequent in women with CNC and breast carcinoma might be considered a "new" manifestation of this disease. As CNC could predispose to breast carcinoma, an adequate screening strategy and follow up should be discussed in affected women.

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OC7.2

The role of the tumour microenvironment in pituitary adenoma angiogenesis

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Introduction
Angiogenesis is regulated by different components of the tumour microenvironment (TME) including cytokines and immune cells. Although angiogenesis has been studied in pituitary adenomas (PAs), the role of individual TME components in PA angiogenesis remains largely unknown. We aimed to characterise the role of the TME components in determining the angiogenesis of PAs, focusing on PA-infiltrating immune cells and the PA-derived cytokine network.
Methods
Different immune cells were studied by immunohistochemistry in 24 human PAs (16 non-functioning PAs (NFPAs) and 8 somatotrophinomas): macrophages (CD68), M2-macrophages (CD163), M1-macrophages (HLA-DR), cytotoxic T lymphocytes (CD8), T helper lymphocytes (CD4), T regulatory cells (FOXP3), B cells (CD20) and neutrophils (neutrophil elastase); endothelial cells were assessed with CD31. Five normal pituitary samples (NP) were included for comparison. Microvessel density and vascular morphological parameters were estimated with *ImageJ* software. Cytokine secretome from these same 24 human PAs were assessed on primary cell culture supernatants using a multiplex immunoassay panel with 42 cytokines.
Results
PAs contained 4× more CD68+macrophages than NP, with a 3-fold increased M2:M1 macrophage ratio, as well as more CD4+T cells but fewer CD8+T cells or neutrophils. Microvessel density and microvessel area were higher in NP than PAs, which also had more round and regular vessels. NFPAs had vessels of increased caliber (higher perimeter and Feret's diameter), occupying an increased area comparing to somatotrophinomas. PAs with more macrophages tended to have higher microvessel density and area, as well as a higher perimeter and Feret's diameter. The M2:M1 macrophage ratio correlated with microvessel density ($P=0.015$) and microvessel area ($P<0.001$) in PAs. PAs with more CD4+T cells had higher microvessel area ($P=0.035$), while PAs with more FOXP3+cells were associated with lower microvessel density ($P=0.021$). PAs with more B cells had more rounded vessels ($P=0.021$). Of the studied PA-derived cytokines and growth factors, only FGF-2 and CXCL10 were significantly associated with microvessel architecture, namely vessel perimeter ($r=-0.407$; $P=0.048$) and area occupied per vessel ($r=0.407$; $P=0.049$), respectively.
Conclusions
Our data suggest that different TME components may influence the angiogenesis of PAs: M2-macrophages appears to play a relevant role in PA angiogenesis, and B, CD4+and FOXP3+lymphocytes may also have a modulatory role in the PA neovascularisation.

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OC7.3

Sterol O-Acyl transferase 1 as a prognostic marker of adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) is a rare endocrine malignancy with an unfavorable prognosis. Despite the poor prognosis in the majority of patients, no improvements in treatment strategies have been achieved. Therefore, the discovery of new prognostic biomarkers is of enormous interest. Sterol-O-acyl transferase 1 (SOAT1) is involved in cholesterol esterification and lipid droplet formation. Recently, it was demonstrated that SOAT1 inhibition leads to impaired steroidogenesis and cell viability in ACC. To date, no studies have addressed the impact of *SOAT1* expression on ACC prognosis and clinical outcomes. We evaluated *SOAT1* expression by quantitative real-time PCR and immunohistochemistry in a tissue microarray of 112 ACCs (Weiss score ≥ 3) from adults treated in a single tertiary center in Brazil. Two independent pathologists evaluated the immunohistochemistry results through a semiquantitative approach (0–4). We aimed to evaluate the correlation between *SOAT1* expression and clinical, biochemical and anatomopathological parameters, recurrence-free survival (RFS), progression-free survival (PFS) and overall survival (OS). SOAT1 protein expression was heterogeneous in this cohort; 37.5% of the ACCs demonstrated strong SOAT1 protein expression (score $ 2), while 62.5% demonstrated weak or absent protein expression (score < 2). Strong SOAT1 protein expression correlated with features of high aggressiveness in ACC, such as excessive tumor cortisol secretion ($P=0.01$), an advanced disease stage [ENSAT 3 and 4 ($P=0.011$)] and a high Ki67 index ($P=0.002$). In multivariate analysis, strong SOAT1 protein expression was an independent predictor of a reduced OS (HR 2.15, CI 95% 1.26 – 3.66; $P=0.005$) in all patients ($n=112$), and a reduced RFS (HR 2.1, CI 95% 1.09 – 4.06; $P=0.027$) in patients with localized disease at diagnosis ($n=83$). Our findings demonstrated that SOAT1 protein expression has prognostic value in ACC and reinforced the importance of investigating SOAT1 as a possible therapeutic target for patients with ACC.
Keywords: adrenocortical carcinoma; prognostic factors; SOAT1; target therapies

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OC7.4

Increased E2F1 mRNA and miR-17-5p expression may predict aggressiveness of pituitary neuroendocrine tumours

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Introduction
E2F1 regulates the expression of genes required for cell cycle progression and apoptosis. miR-17-5p regulates expression of *E2F1*. Both miR-17-5p and *E2F1* have been described deregulated in cancer but they have been scarcely studied in human pituitary neuroendocrine tumours (PitNETs).
The aim of the present study was to find biomarkers of aggressiveness in PitNETs and report the correlation between *E2F1* and miR-17-5p in the regulation of the pituitary tumorigenesis.
Methods
In this cross-sectional descriptive study, we evaluated the expression of *E2F1*, c-myc and two microRNAs of miR-17~92 cluster (miR-20a and miR-17-5p) by qRT-PCR in 60 human PitNET samples: 29 gonadotrophs (GT), 15 functioning somatotrophs (fST), 8 functioning corticotrophs (fCT) and 8 silent corticotrophs (sCT). Clinical, radiological and pathological data were recovered to determine the pre-operative behavior of the tumour. We defined invasiveness if the tumour invaded one of the cavernous or sphenoid sinus. We defined aggressiveness depending on the invasiveness of the tumours and the Ki-67 expression.
Results
E2F1 and c-myc demonstrated different expression in PitNETs depending on subtypes ($P=0.000$ and 0.004 respectively). Specifically, GT and sCT showed overexpression of E2F1 compared to the functioning variants (fST and fCT). In the whole series, *E2F1* was more expressed in invasive than in non-invasive tumours ($P=0.004$). Moreover, *E2F1* ($P=0.001$) and miR-17-5p ($P=0.011$), were overexpressed in tumours with high grade of aggressiveness in the whole series.
Conclusions
We confirm the deregulation of *E2F1* and c-myc in the pathogeneis of PitNETs, with different behavior depending on their subtypes. Moreover, *E2F1* and miR-17-5p could be good markers of PitNET aggressiveness.

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OC7.5

Differential adrenal toxicity of SOAT1-inhibitors

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Background
Mitotane is the only approved treatment for advanced adrenocortical carcinoma and was shown to inhibit Sterol-O-Acyl transferase 1 (SOAT1) which leads to the depletion of cholesterol esters and increase of free cholesterol in the ACC cell line H295R. Downstream activation of the endoplasmic reticulum stress (ER-stress) pathway results in decreased adrenocortical cell viability.
Aim
To better characterize the effects of SOAT1 inhibition in ACC, four human cell lines (H295R, MUC-1, CU-ACC1 and CU-ACC2) were treated with the SOAT1 inhibitors SOATi) mitotane, nevasimibe, AZD 3988 and Sandoz 58-035.
Methods
SOAT1 inhibition was quantified *in vitro*, ER-stress marker expression by qPCR and WB, cell viability by cell titer glo-assay, SOAT1 knockdown (KD) by siRNA and steroid hormone synthesis by LC-MS/MS.
Results
Mitotane, nevasimibe, AZD 3988 and Sandoz 58-035 inhibited SOAT1 in NCI-H295R cells with IC_{50} of 1.3 µM, 3.1 nM, 0.9 nM and 13 nM, respectively. Expression of ER-stress markers was activated by mitotane, nevasimibe, only poorly by AZD 3988 and not at all by Sandoz 58-035. Sandoz58-035 did not impair viability of any ACC cell line. H295R cells were most responsive to SOAT1 inhibition, while MUC-1 cells were least responsive, with EC_{50}>100µM for all inhibitors. Only mitotane efficiently blocked cortisol secretion in the two highly cortisol-secreting cell lines H295R and CU-ACC1. KD of SOAT1 in NCI-H295R cells did not affect the response to mitotane treatment.
Conclusion
Although SOAT1 inhibition was confirmed for all compounds, downstream effects on ER-stress markers and cell viability exhibit marked differences. SOAT1 expression does not affect mitotane responsiveness in H295R cells, suggesting targets different from SOAT1 are relevant for *in vitro* cytotoxicy. Their identification may lead to novel ACC treatments.

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OC7.6

Llaser ablation vs radiofrequency ablation for benign non-functioning thyroid nodules: six-month results of a randomised, parallel, open-label, trial (LARA trial)

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Background
No direct prospective studies comparing laser ablation (LA) and radiofrequency ablation (RFA) for debulking benign non-functioning thyroid nodules (BNTNs) exist. We aimed to compare the efficacy and safety of both techniques in patients with solid or predominantly solid BNTN.
Methods
This six-month, single-use, randomized open label parallel trial compared the following primary endpoints between the RFA and LA groups six months after treatment: (1) nodule volume reduction expressed as a percentage of nodule volume at baseline; (2) proportion of nodules with more than 50 % reduction (successful rate). We enrolled subjects with a solitary BNTN or dominant nodule characterized by pressure symptoms/cosmetic problems or patients without symptoms who experienced a volume increase >20% in one year. Nodules underwent core needle biopsy (CNB) for diagnosis. Patients were randomly assigned (1:1) to receive LA or RFA. Safety was assessed in all randomly assigned participants.
Results
Sixty patients were randomly assigned to receive either RFA or LA (1:1) between January 2016 and November 2018. Both groups were similar in basal nodule volume, thyroid function, histology, symptoms/cosmetic score, and procedure time. At six months, the nodule volume reduction was 64.3% (95% confidence interval 57.5 – 71.2%) in the RFA group and 53.2% (47.2 – 95.2%; $P=0.02$) in the LA group. This effect was also confirmed in the linear regression model adjusted for age, baseline volume, and proportion of cellular component (LA vs RFA percent change Delta=−12.8, $P=0.02$). No significant difference was observed in success rate 6-month after treatment (RFA vs LA: 86.7% vs 66.7%, $P=0.13$) or in thyrotropin level between the groups. Although improved, no significant

difference was observed between RFA and LA for compressive symptoms (RFA: 2.13 vs 3.9, $P<0.001$; LA: 2.4 vs 3.87, $P<0.001$) and cosmetic score (RFA: 1.65 vs 2.2, $P<0.001$; LA: 1.85 vs 2.2, $P<0.001$). The adverse event rates (local pain, dysphonia, thyrotoxicosis, fever, hematoma) were 37% ($n=11$) and 43% ($n=13$) for RFA and LA, respectively, with no requirement for hospitalization.
Conclusion
While the success rate was similar in the RFA and LA groups, RFA achieved a significantly larger nodule volume reduction at six months.

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OC7.7

A rare case of lynch syndrome in a patient with metastatic malignant paraganglioma with SDHA mutation

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Paragangliomas (PGLs) and pheochromocytomas (PCCs) are rare tumors that arise from the neuroendocrine tissue along the paravertebral axis with the ability to secrete cathecolamines. Up to 33% of these tumors may be hereditary either alone or as a component of a multiple tumor syndrome. Germline *SDHA* mutations are relatively frequent (7.6%) in patients with genetically unexplained PGL, even in the absence of familial or clinical indications for inherited PGL. Most of *SDHA* mutation carriers presented with an apparently sporadic head and neck PGL and extra-adrenal PGL. Lynch Syndrome (LS) is one of the most common cancer susceptibility syndromes. Individuals with Lynch syndrome have a 50%–70% lifetime risk of colorectal cancer, 40%–60% risk of endometrial cancer, and increased risk of several other malignancies. It is caused by germline mutations in the DNA mismatch repair genes MLH1, MSH2, MSH6 or PMS2. We present the case of a woman who underwent surgery in 2008 for retroperitoneal paraganglioma removal. No previous medical history was reported. Ten years later, she presented with mechanical-back pain and headaches. Initial imaging included MRI of the abdomen and lumbar spine and showed bone metastasis in T10-T11-T12. Laboratory investigations included 24-h fractionated urinary catecholamines and metanephrines supporting a functional tumor (plasma normetanephrine 425 mg/24 h and urine normetanephrine 976 mg/24 h). She was treated initially with phenoxibenzamine 20 mg daily in 2 doses and stereotactic body radiation therapy (SBRT), completing a course of 57 Gy in 8 fractions. Genetic testing was also performed. It revealed the expression of 2 mutations in heterozygosis, in both genes SDHA (v481fs* R31) and PMS2. The patient had not suffered from any disease associated with Lynch syndrome until now. It is not common to find these 2 mutations in the same person; in fact, there is not any case described before in the literature. This case report enhances the importance of clinical follow-up in pheochromocytomas and paragangliomas and encourages us to perform genetic testing to prevent the development of malignancies in people who carries oncogenic mutations.

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Environmental Endocrinology

OC8.1

The mosaic effects of endocrine disrupting chemicals mixtures on thyroid hormone levels: experimental study

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The lifelong exposure to mixtures of endocrine disrupting chemicals raises serious concerns about their deleterious effects on human health. Polychlorinated biphenyls (PCBs) had widespread use in numerous industrial applications, and were massively produced for several decades. After the discovery of the adverse effects of PCBs in the 1970s, brominated flame retardants (BFRs) were established as the major chemical flame retardant. Both chemicals persist in the environment and biomagnify in the food chain, hence their cocktail effect on thyroid gland can be assumed.
This experimental study was aimed to assess effects of repeated relatively low doses (corresponding low to high environmental human exposures) of these persistent organic pollutants on thyroid homeostasis in adult animals. Rats were randomized into control and treatment groups. Animals were treated by oral gavage for 28 days with either PCBs solution in corn oil or polybrominated diphenyl ether (BDE-209) suspension in dimethyl sulfoxide, or their combination. Animal groups were receiving BDE-209 suspension or commercial mixture of Aroclor 1254 at five different dose levels for each chemical. Nine groups were receiving different combinations of BDE-209 and PCBs. Treatment of all animals was performed by oral gavage, each day, during 28 days. Thyroid hormones were investigated in serum samples obtained from blood samples collected at necropsy.
Applied doses of PCBs induced dose dependent decrease in T4, while BDE 209 caused increase in T4 and decrease in T3 levels, compared to respective controls. However, no interaction at tested dose levels of PCBs and BDE-209 were observed implying that PCBs and BDE-209 as chemicals which act by similar modes at the level of thyroid homeostasis, exert additive effects in mixture.
The study implicates that exposure to low, environmental doses of these chemicals interferes with thyroid function and raises an issue of their additive thyroid toxicity in mixtures.

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OC8.2

Air pollution and incidence of hypertension in spanish adults Di@bet.es study

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Introduction
The metabolic risk associated with air pollution could vary according to the specific pollution levels of each area, as well as factors related to lifestyle (diet, activity physical, socioeconomic status, tobacco), other exposures, comorbidities etc.. and has been insufficiently evaluated in our country.
Objective
To study the association between long term exposure to air pollution (measured as PM concentrations) and the incidence of hypertension in a disease free sample representative of the adult population of Spain (di@bet.es).
Methods
The study population was composed of 1103 individuals, participants in the nation-wide population based cohort study di@bet.es, free of hypertension at baseline (2008–2010) who completed the follow up exam of the cohort (2016–2017) with complete clinical information and blood pressure measurements available for analyses. Mean follow up time was 7.4 ± 0.6 years.
Exposure Assessment
Cohort participants were assigned air pollution exposures for particulate matter $<10\,\mu m$ (PM10) and $<2.5\,\mu m$ (PM25) during follow-up (2008–2016) obtained through modeling combined with measurements at air quality stations (CIEMAT).
Diagnose of Hypertension
Hypertension was considered if there was a previous clinical diagnose of hypertension and/or systolic blood pressure was ≥140 mmHg and/or diastolic blood pressure was ≥90 mmHg.
Results
In the table we present crude and multivariate adjusted Odd Ratios for developing Hypertension during follow up according to PM10 and PM2.5 cuartiles.

	PM 10 (μg/l)				
	12.21–16.95	16.96–20.00	20.01–22.79	22.80–30.18	*P* for trend
Number at risk	278	280	279	266	
Number developing HT	63	61	74	84	
OR crude (95% CI)	1 (reference)	0.95 (0.64–1.42)	1.23 (0.84–1.81)	1.58 (1.08–2.31)	0.008
OR multivariate (95% CI)	1 (reference)	1.08 (0.70–1.67)	1.36 (0.88–2.12)	1.86 (1.19–2.91)	0.005
	PM 2.5 (μg/l)				
	7.25–9.31	9.32–10.77	10.78–11.79	11.80–16.49	
Number at risk	280	275	279	269	
Number developing HT	68	60	68	86	
OR crude (95% CI)	1 (reference)	0.87 (0.59–1.29)	1.00 (0.68–1.48)	1.47 (1.01–2.13)	0.032
OR multivariate (95% CI)	1 (reference)	0.96 (0.63–1.49)	1.00 (0.64–1.56)	1.67 (1.07–2.59)	0.029

Multivariate ORs were calculated by logistic regression adjusted for age, gender, ethnicity, education level, MedScore, SF-IPAQ BMI and municipality population.

Conclusions

Our study shows an association between PM concentrations and the incidence of Hypertension in Spain even with pollution levels below the air quality levels currently established. These data reinforce the need for measures to improve air quality in our country.

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OC8.3

Comparative histopathology of endocrine glands in phthalate exposed male Wistar rats unveil the vulnerability of adrenal gland and augmented by molecular docking

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Limited research has been conducted on adrenal gland as target of endocrine disrupting chemicals (EDCs). Moreover, studies on steroidogenesis as the target of EDCs has also attracted lesser attention compared to other metabolic pathways. We studied the effects of two extensively used phthalate esters viz., di-ethyl hexyl phthalate (DEHP) and di-butyl phthalate (DBP) on the adrenal gland in Wistar rats and checked its susceptibility against the exposure of these extensively used phthalates categorized as EDCs. Male rats were divided into seven groups ($n=6$). Group I (control) received only corn oil (as vehicle). Group II, III and IV were treated daily with DEHP at the dose of 250, 750 and 1500 mg/kg-BW respectively *per os* for 14 days. Group V, VI and VII were treated with daily dose of DBP 100, 500 and 1000 mg/kg-BW respectively *per os* for 14 days. The comparative histological observation of endocrine glands i.e., pituitary, pineal, thyroid, parathyroid, adrenal gland and testes unveil that changes in adrenal gland towards the DEHP and DBP were more remarkable compared to other endocrine glands. Glucocorticoid biosynthesis pathway in adrenal gland was analyzed by molecular docking of DEHP and DBP with the enzyme proteins involved in the pathway using Maestro Schrodinger 9.4 software. It showed the potential of DEHP and DBP to inhibit these proteins comparable to the known inhibitors of enzymes involved. The present study used a novel approach of *in silico* and *in vivo* to elucidate the sensitivity of adrenal gland towards EDCs through the analysis of the sensitivity of adrenal steroidogenesis on exposure to two widely distributed phthalates with environmental and human health risk potential.

Keywords: glucocorticoid biosynthesis pathway, endocrine glands, phthalate esters, molecular docking.

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OC8.4

Cigarette smoking and the risk to develop symptoms of Hashimoto's thyroiditis

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Introduction

Hashimoto's thyroiditis (HT) is a complex disease which is caused by genetic as well as environmental factors. While the genetic predisposition to HT has been extensively investigated, the influence of most environmental factors still needs to be evaluated. Based on our previous study, we did not find any correlation between HT and the fact of cigarette smoking or the number of pack-years. We did, however, find a significant correlation between the age of smoking discontinuation and the age of HT onset. However, in this previous study, the number of patients for which we have obtained data on smoking discontinuation, was very sparse; therefore, no unequivocal conclusions could have been made.

Aim

The aim of our study was to verify the correlation between the age of smoking discontinuation and HT diagnosis.

Methods

In our first study, we included 35 HT patients who have declared to have stopped smoking in the past. The verification study included 48 patients. Stepwise regression analysis was used to predict the dependence of the age of HT diagnosis with gender, age of smoking discontinuation, TSH at diagnosis, and anti-TPO at diagnosis.

Results

In patients who had discontinued smoking at the age of 39 years or more, the diagnosis of HT was predominantly made after the discontinuation of smoking. No such regularity was observed for patients who had stopped smoking before the age of 39 years. In their case, the diagnosis of HT was made similarly often before and after the discontinuation of smoking. The patients' gender and biochemical parameters at diagnosis were not significantly correlated with the age of HT onset.

Conclusions

We concluded that neither smoking nor its discontinuation has a significant impact on the onset of HT symptoms in patients aged less than 39 years before smoking discontinuation. However, in the vast majority of our HT patients who had stopped smoking at a later timepoint, it seemed as if stopping smoking was a trigger of HT symptoms that would be indicative of the disease. It remains to be evaluated whether this is a straight-forward correlation or whether other factors like hormonal changes or the ability to deal with stress in the older patients might have been involved in the observed correlation.

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OC8.5

Effects of perinatal exposure to triclosan on neuronal development and behavior of mice

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There have been raising concerns in the effects of endocrine disrupting chemicals like triclosan (TCS) on the embryo development. Triclosan (TCS) is commonly present in household and personal wash products We hypothesize that exposure to TCS during early stage of development could alter brain development affecting behavior. To test this hypothesis, primary cortical neurons were exposure to TCS with/without estrogen antiestrogen ICI 182780 from day in vitro 1 to 4. We also address whether maternal TCS-exposure at dose 10 mg/kg and 100 mg/kg during pregnancy and lactation, affects neurobehavioral development in the offspring generation. We found that TCS impaired to growths of dendrite and axon by reducing the average

dendrite lengths and number of both axon and dendrite. In the present of ICI, the effects of TCS on neurite growth are recued. At six weeks of age, the spatial learning and reference memory in offspring derived from dams exposed to TCS were impaired. Furthermore, TCS-treated groups displayed cognition dysfunction in novel test and impairments in sociability and social novelty preference in three-chamber social test. In addition, TCS-treated groups increased anxiety-like behavior in open field test. Moreover, TCS-treated groups exhibited deficits in nesting behavior. However, there was no significant difference in depression-like behavior in tail suspension test and forced swimming test. Our data demonstrate that perinatal exposure to TCS induces the neurodevelopment disorder, causes abnormal in social behavior, cognitive impairment, and deficits in spatial learning and memory in offspring.

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OC8.6

Temporal and spatial trends of operated cryptorchidism in France and environmental hypotheses: a nationwide study from 2002 to 2014

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Introduction
Santé publique France develops a national epidemiological monitoring program to study health indicators related to endocrine disruptor exposure. Based on the weight of evidence, cryptorchidism was selected for this purpose. In this study, we aimed to analyze temporal, spatial and spatio-temporal trends of cryptorchidism during the period 2002–2014 in France, and explore and/or generate environmental hypotheses.
Methods
We built an indicator reflecting incident operated cryptorchidism in boys under the age of 7, using the data of the French National Hospital Discharge Database (PMSI). We fitted temporal, spatial and spatio-temporal models to describe trends of the risk of cryptorchidism at the department and at the postal code scale. We used Kulldorff's spatial scan statistic and Tango's flexibly shaped spatial scan statistic to identify spatial clusters at the postal code scale. We studied all types of cryptorchidism and bilateral cases separately. We searched for demographic, economic and environmental shared characteristics within clusters to discuss environmental hypotheses.
Results
We identified 91400 new cases of operated cryptorchidism in boys under the age of 7 years, including 9799 (10.7%) bilateral cases. The observed incidence was equal to 2.14 /1000 in 2002 and to 2.81/1000 in 2014. In the study period, the estimated increase of operated cryptorchidism incidence was equal to 37.1% (31.5%; 42.9%), especially among boys under 2 years and bilateral cases. An increase was observed in all departments, including ultramarine territories. The risk of cryptorchidism presents structured spatial heterogeneity. We detected 24 spatial clusters scattered in Metropolitan France. Low socio-economic levels were often observed in the cluster areas. Potential environmental exposures included mining activities (8/24 clusters), metallurgy (17/24 clusters) and mechanics (16/24 clusters). We also detected 21 spatial clusters of bilateral operated cryptorchidism, in the same areas and in a few agricultural areas.
Discussion, conclusion
To our knowledge, this is the first descriptive study on cryptorchidism addressing the issue of environmental exposure nationwide, with a large sample. As regards environmental hypothesis, this is an exploratory study, with limits due to the indicator built from hospital discharges and lack of individual data. Among some of the identified, environmental exposures related to mining and metallurgy could have induced persistent environmental pollution to metals, metallurgy inducing in addition dioxins and PCBs. This study analysis should be considered as a hypothesis-generating process for future research studies.

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Reproductive and Developmental Endocrinology

OC9.1

Identification of a novel hypothalamic miRNA/Kisspeptin pathway as pathophysiological mechanism and putative target for management of obesity-induced hypogonadism

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Among its numerous comorbidities, obesity is often linked to central hypogonadism in men, i.e., low circulating levels of gonadotropins and testosterone. While this condition of obesity-induced hypogonadism (OIH) is frequently neglected, it has been suggested to contribute to the metabolic complications of male obesity. However, the mechanisms of OIH, and even its actual role in the metabolic alterations of obesity remain ill defined. Our recent data suggest that OIH is bound to suppression of the hypothalamic Kiss1/kisspeptin system, which would lower gonadotropin levels and, thereby, testosterone in obese males. Yet, the mechanisms for Kiss1 suppression in obesity remains unknown. Our recent findings suggest that microRNAs might operate as putative regulators of Kiss1. Here, we identify a novel miRNA pathway regulating kisspeptin expression, and assess its potential contribution to OIH. Bioinformatic prediction of miRNA regulators of the *KISS1* gene were conducted with several algorithms, searching for putative seed regions at the 3' untranslated region (3'UTR) of *KISS1*. For selection, miRNA candidate(s) had to meet the following criteria: 1) to be identified in at least two databases; 2) to display evolutionary conservation of its seed regions; and 3) to be sensitive to metabolic regulation, according to previous literature. Based on these criteria, miR-A (*anonymized due to ongoing patent protection*) was selected as a robust putative modulator of *KISS1*. Luciferase reporter assays confirmed a repressive interaction of miR-A at the 3'UTR of *KISS1*. Hypothalamic expression of miR-A was increased in obese male rats displaying OIH. Moreover, in vivo administration of a target-site blocker (TSB), tailored to specifically prevent the repressive interaction of miR-A at the 3'UTR of *Kiss1*, significantly ameliorated the reproductive and metabolic alterations observed in a rat model of OIH. Thus, while OIH rats showed severe suppression of T and gonadotropin (LH) levels, together with notable metabolic alterations (glucose intolerance, insulin resistance), elevated systolic blood pressure and severe inflammation, TSB administration not only restored T and LH levels, and enhanced hypothalamic kisspeptin, but improved also the metabolic alterations seen in OIH rats, even more effectively than pharmacological treatments with either kisspeptin or T. In sum, we provide herein preclinical evidence for a major role of a central miR-A/kisspeptin pathway in the generation OIH. This pathway might be a suitable target for the management of central hypogonadism linked to obesity, and its major metabolic complications.

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OC9.2

Kisspeptin as a biomarker for pregnancy complications

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Background
Placentation (invasion of the placenta into the maternal endometrium of pregnancy known as the decidua) is hypothesised to be critical for healthy placental function and is abnormal in two thirds of miscarriage. Kisspeptin has emerged as a putative regulator of physiological placentation; it is highly expressed in placental syncitio-trophoblasts, whereas its receptor is expressed in both syncitio- and cyto-trophoblasts, such that kisspeptin is hypothesized to play an important paracrine role to regulate placentation. Circulating kisspeptin levels are considerably raised during healthy pregnancy and are reduced in women with miscarriage.

Aim
We aimed to investigate the utility of circulating kisspeptin levels in the assessment of pregnancy complications and determine whether kisspeptin provides additional diagnostic information compared to beta human chorionic gonadotropin (βhCG) alone.
Methods
This study was performed in collaboration with the Early Pregnancy Outcome Study (EPOS), which aims to identify novel pregnancy biomarkers. Women were invited to attend every fortnight for blood-sampling, clinical and ultrasound assessment during the first trimester, and repeated during the second and third trimesters. Asymptomatic women with healthy pregnancy ($n=265$) provided 960 blood-samples. Women with pregnancy complications including miscarriage ($n=95$), pre-eclampsia (PET; $n=24$), pregnancy induced hypertension (PIH; $n=14$), gestational diabetes (GDM; $n=41$), preterm birth (PTB; $n=14$) and intrauterine growth restriction (IUGR; $n=24$) provided 569 blood-samples.
Results
Gestation-adjusted circulating kisspeptin and βhCG levels were lower, by 66% and 57%, respectively, in women with miscarriage compared to healthy pregnant controls ($P<0.0001$). Area under ROC curve for diagnosis of miscarriage was greater for the combination of both kisspeptin and βhCG together (0.92) than for either measure alone (βhCG 0.859, kisspeptin 0.874). An adjusted logistic regression model revealed that every 100 pmol/l increase in plasma kisspeptin levels reduced the odds of miscarriage by 42%. Gestation-adjusted kisspeptin levels were lower in women with GDM ($P=0.002$), or IUGR ($P<0.0001$), and higher in women with PTB ($P=0.004$). Kisspeptin increased with gestation greater in PET ($P=0.008$) and PIH ($P<0.0001$) than in healthy controls.
Conclusions
Plasma kisspeptin is a promising biomarker for pregnancy complications and provides additional diagnostic capability over that provided by βhCG alone.

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OC9.3

Association between an AMH promoter polymorphism and serum AMH levels in PCOS patients

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Introduction
Polycystic ovary syndrome (PCOS), the most common endocrine disorder in women of reproductive age, is diagnosed based on three criteria, including a polycystic ovarian morphology. Moreover, women with PCOS have elevated serum Anti-Müllerian Hormone (AMH) levels, a hormone known to correlate with follicle number. In addition, AMH production per follicle is suggested to be higher in PCOS. Little is known about AMH gene regulation. Hence, this study aims to investigate the regulation of AMH gene expression in PCOS patients. We have taken a genetic approach through association analysis and performed *in silico* analysis of common variants in the human AMH promoter. Associated variants were analyzed *in vitro* to assess the functional impact.
Methods
A cohort of 700 Caucasian PCOS women, diagnosed by the Rotterdam criteria, were included. All common two-allelic single nucleotide polymorphisms (SNPs), located in the region Chr19:2,245,353–2,250,827bp, were selected. AMH levels were measured with the picoAMH assay (Ansh Labs, Houston, Texas, USA) and presented as median (first–third quartile). The association between SNPs and serum AMH levels was analyzed by regression and allele carrier model analyses. KK1 cells were used to assess the functional effects of associated variants.
Results
We assessed 11 SNPs in 700 Caucasian PCOS patients. Polymorphism rs10406324 was associated with AMH levels in the regression analysis. This effect remained present when adjusted for age, BMI, and follicle count ($\beta=-0.52$, $P=6.08e-07$). Similar results were obtained in a carrier model analysis [AA: $n=645$, 8.29 ng/ml (5.20–12.81) vs AG/GG: $n=54$/n=1, 5.57 ng/ml (3.40–9.98), $P=1.47e-03$]. Results were replicated in an independent cohort of 321 PCOS patients of European ancestry ($P=2.59e-03$ and $P=6.2e-03$, respectively). Stratification by BMI in lean (<25 kg/m^2) and obese (>30 kg/m^2) patients showed that the association was only present in obese PCOS patients [$P=0.01$ (AA: $n=162$, AG/GG: $n=14$)], but not in lean PCOS patients [$P=0.11$ (AA: $n=322$, AG/GG: $n=22$)]. *In silico* analysis suggested a decreased binding affinity of the transcription factor SF1 to the minor allele G variant. Subsequently, functional analysis showed a significant decrease in basal activity of the AMH promoter construct containing the G variant ($P=0.04$), and a lower SF1-induced activity compared to the A variant ($P=8.7e-03$).
Conclusion
We have identified a functional AMH promoter polymorphism rs10406324 that is associated with lower serum AMH levels in obese PCOS women. These findings suggest that the genetic context should be taken into consideration when establishing an AMH cutoff value to diagnose PCOS.

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OC9.4

Demonstration of follicle-stimulating hormone receptor and G protein-coupled estrogen receptor heteromers in vitro via BRET and super-resolution imaging

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Introduction
The developmental stages of the ovarian follicle are characterized by changes of gonadotropin and steroid hormone receptor expression and their potential interactions on the surface of granulosa cells. In this study *in vitro*, we aim to evaluate whether the co-existing follicle-stimulating hormone receptor (FSHR) and G protein-coupled estrogen receptor (GPER) form heteromers, which may play role in selecting the dominant ovarian follicle.
Methods
FSHR-GPER interactions was evaluated in transfected HEK293 cells by bioluminescence resonance energy transfer (BRET) and photo-activated localization microscopy using photoactivatable dyes (PD-PALM). Molecular modelling of FSHR-GPER heterodimers identified the sixth and seventh transmembrane segments (T6, T7) of both receptors as a potential heteromer interface. Seven T6 and eight T7 GPER putative interaction amino acid residues were mutated to alanine (mutGPER). Intracellular Ca^{2+} levels were measured by aequorin-dependent calcium assay (AEQ-GFP) and BRET.
Results
In order to evaluate its functionality and compare it to the wild-type receptor (wtGPER), wt or mutGPER were transiently expressed in HEK293 cells and demonstrated to both mediate estradiol (E_2)-induced intracellular Ca^{2+} increase (two-way ANOVA; $P<0.0001$; $n=8$; mean±S.E.M). FSHR-wtGPER dimerization was demonstrated by BRET in HEK293 cells transiently transfected with a fixed amount of Rluc8-tagged FSHR and increasing doses of wtGPER-Venus. The BRET signal logarithmically increased together with the acceptor concentration (non-linear regression; $r^2=0.876$; $n=4$; mean±S.E.M), revealing a specific heretomeric interaction between the two receptors. Further confirmation of the FSHR-wtGPER complexes at the cell surface was obtained by super-resolution PD-PALM imaging in cells co-expressing HA-tagged FSHR and FLAG-tagged wtGPER. We found FSHR and wtGPER both form monomers and homomers in equivalent amounts, however, while FSHR formed both dimers and a range of low to higher order homo-oligomers, GPER-GPER associations were primarily homodimer. FSHR-wtGPER heteromers were also observed with heterodimers as the predominant form (15% +/− 2.2, Mean±S.E.M; $n=8$). The ability of mutGPER to associate with FSHR was first determined by BRET, which demonstrated no specific BRET interaction (linear regression; $r^2=0.014$; $n=4$; mean±S.E.M). Furthermore, a fourfold decrease in the percentage of

heterodimeric structures in the cell surface were found by PALM ($n=3$), indicating the failure of heteromeric assembly between FSHR and mutGPER at the plasma membrane.
Conclusion
We demonstrated for the first time the physical interaction of FSHR-GPER *in vitro*, and identified a molecular heteromer interface, which could be exploited to understand the role of this heteromer in granulosa cell physiology.
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OC9.5

Genetic dissection of spermatogenic arrest through whole exome analysis: Clinical implications for the management of azoospermic men
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Background
Non-obstructive azoospermia affects about 1% of men and has a multifactorial etiology with heterogeneous testicular histology. Pure spermatogenic maturation arrest (MA) is a relatively rare NOA phenotype but its clinical relevance is high, since patients affected by MA should not undergo invasive testis surgery. A clear-cut distinction between MA and other spermatogenic disturbances leading to azoospermia is not possible with the currently available clinical tools. Consequently, testis biopsy (TESE), is offered to all NOA patients as the only treatment option to recover spermatozoa for subsequent in vitro fertilization. MA is of polygenic nature and in >60% of cases the etiology remains unknown.
Methods
We aimed to identify the underlying genetic cause of MA in 17 patients using whole exome analysis.
Results
Rare or novel LoF mutations (homozygous or compound heterozygous) were identified in 5 novel genes (*TERB1, MSH4, ADAD2, SHOC1* and *RAD21L1*) for which mouse KO models are concordant with the human phenotype. Our meiotic studies in the testis biopsy of the mutation carriers provided detailed characterization of the functional consequences of the variants, supporting their causative role in MA. In addition, 8 patients carried pathogenic variants in 7 previously reported genes - *TEX11, TEX14, MEIOB, MEI1, DMRT1, STAG3* and *SYCE1*. Thanks to our study, the clinical significance of these genes can now be upgraded to strong or definitive level, therefore they can be proposed for diagnostic purposes. In four cases, infertile or fertile brothers were available, and the recessive genotype segregated with azoospermia. Interestingly, both of our patients with variants in *MSH4* and *SYCE1* had at least one infertile sister with suspected premature ovarian insufficiency (POI).
Conclusions
The diagnostic yield of our exome analysis was 76%. This data is unique in this field and have implications for the understanding of human meiosis and its defects. In addition, we report novel genetic links between azoospermia and POI and propose three novel MA genes (*ADAD2*, *RAD21L1* and *TERB1)* as potential candidates for POI. Since the reported gene defects were all associated with pure MA (no mature spermatozoa found in the testis), our study contributes substantially to the development of a pre-testis biopsy gene panel with prognostic value for sperm retrieval.
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OC9.6

Testosterone replacement therapy of opioid induced male hypogonadism improved body composition but not pain perception A double-blinded, randomized and placebo-controlled trial
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Background
Hypogonadism is prevalent during opioid treatment, but the effect of testosterone replacement treatment (TRT) on body composition, pain perception, and adrenal function is unclear.
Purpose
To measure changes in body composition, pain perception, quality of life and adrenal function after TRT or placebo in opioid treated men with chronic non-malignant pain.
Methods
Double-blinded, placebo-controlled study in 41 men (>18 years) with total testosterone <12 nmol/l were randomized to 24 weeks TRT (Testosterone undecanoate injection 3 times/6 months, $n=20$) or placebo (placebo-injections, $n=21$).
Outcomes
Body composition (lean body mass and fat mass assessed by DXA), clinical pain intensity (numerical rating scale), and experimental pain perception (quantitative sensory assessment), quality of life (SF36), and adrenocorticotrophic hormone (ACTH) test. Data were presented as median (quartiles). Mann Whitney tests were performed on delta values (24–0 weeks) between TRT and placebo.
Results
The median age was 55 years (46; 59) and total testosterone before intervention was 6.8 (5.0; 9.3) nmol/l. TRT was associated with change of testosterone levels 12.3 (7.0; 19.8) nmol/l ($P<0.001$ vs placebo), increased lean body mass 3.6 (2.3; 5.0) kg vs 0.1 kg (−2.1; 1.5) during TRT vs placebo and decreased total fat mass −1.2 (−3.1; 0.7) kg vs 1.2 kg (−0.9; 2.5) kg, both $P<0.003$. Changes in pain perception, SF36, and ACTH stimulated cortisol levels were non-significantly changed during TRT compared with placebo.
Conclusions
Six months TRT improved body composition in men with opioid induced hypogonadism without significant changes in outcomes of pain perception, quality of life or adrenal function.
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OC9.7

Abstract withdrawn.

Young Investigator Awards

YI1

A mixed nutrient preload attenuates glucose-induced endothelial dysfunction in individuals with abnormal glucose tolerance
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Background
Postprandial hyperglycemia is an independent risk factor for cardiovascular disease and all-cause mortality. This excess cardiovascular risk may be partly explained by the impairment in endothelial function that typically follows an acute increase in plasma glucose levels. Recently, nutritional interventions focused on the sequence of macronutrient consumption within the meal have been proposed to normalize postprandial glycemia in subjects with abnormal glucose tolerance (AGT). We therefore aimed to establish whether and by which mechanisms a protein- and fat-rich nutrient preload attenuates glucose-induced endothelial dysfunction in individuals with AGT.
Methods
In this randomized controlled trial, the endothelial function was assessed by the reactive hyperemia index (RHI) using an EndoPAT device at fasting, 60 min and 120 min during two 75 g oral glucose tolerance tests (OGTTs) preceded by either a mixed nutrient preload (one boiled egg, 50 g parmesan cheese, 300 ml water) or a water preload (500 ml water; control OGTT). A total of 30 volunteers were recruited, including 22 patients with impaired glucose tolerance (IGT, $n=13$) or diet-controlled type 2 diabetes (T2D, $n=9$), who were classified as AGT. A group of 8 subjects with normal glucose tolerance underwent the control OGTT and was used as reference. Plasma glucose, insulin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), glucagon, free fatty acids (FFA), arginine, branched chain amino acid (BCAA), and total amino acids (AA) were measured during the tests.

Results
The RHI negatively correlated with fasting plasma glucose ($r=-0.29$, $P=0.04$). During the control OGTT, the RHI decreased by 9% ($P=0.02$) and its deterioration was associated with the time-course of plasma glucose levels ($\beta=-0.03$, $P=0.015$). In individuals with AGT, the nutrient preload attenuated the decline in the RHI ($P=0.04$) and markedly reduced postprandial glycemia ($P=0.0003$) compared with the control OGTT. The beneficial effect of the nutrient preload on the RHI was proportional to the improvement in glucose tolerance ($r=0.52$, $P=0.02$). Furthermore, it was associated with the increase in plasma GLP-1 ($r=0.47$, $P=0.04$) and arginine levels ($r=0.64$, $P=0.04$).
Conclusions
A mixed protein- and fat-rich nutrient preload attenuates postprandial endothelial dysfunction in individuals with AGT by lowering plasma glucose excursions and by increasing GLP-1 and arginine levels, both of which are known upregulators of the nitric oxide vasodilator system.

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YI2

Transcriptomic response of mouse thyroid to iodine by upregulating Nrf2-dependent and independent pathways

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Introduction
Nrf2 (Nfe2l2) is a transcription factor that regulates a series of cytoprotective and antioxidant enzymes. Upon exposure to oxidative or electrophilic stress, Nrf2 enters the nucleus and induces its target genes expression. Follicular thyroid cells have physiologically high levels of reactive oxygen species as oxidation of iodine is essential for iodination of thyroglobulin and thyroid hormones synthesis. We have shown previously that Nrf2 pathway is active in thyroid and regulates the transcription of thyroglobulin.
Hypothesis
We thus hypothesized that the response of thyroid to iodine excess should comprise Nrf2-dependent and -independent pathways.
Methods
To this end, 3 months-old male C57Bl6J wild-type (WT) or Nrf2 knockout (Nrf2KO) mice were exposed to 0.05% sodium iodide in their water for 7 days. Thyroids were used for RNA extraction; RNA-seq was performed by Exiqon, with a fold-change cutoff set at 2. Representative genes of the enriched pathways were quantified by qPCR to validate RNA-seq results. Pathway analysis of the differentially expressed genes was performed using the Ingenuity Pathway Analysis (IPA) software. Pathways that were enriched with a p-value <0.05 were considered significant.
Results
828 genes were differentially expressed in response to iodine exposure; 66% were upregulated, as were most of the highly enriched pathways (related to inflammatory-immune response, antioxidant response, xenobiotic metabolism, platelet activation and calcium signaling). About 300 genes were differentially expressed between WT and Nrf2KO mice; highly enriched pathways were related to glutathione and xenobiotic metabolism, Ahr signaling and Nrf2 signaling and were all downregulated in Nrf2KO mice. Analysis of the potential upstream regulators of these highly enriched pathways revealed that Nrf2 and NfkB are main regulators of the antioxidant and inflammatory response induction upon iodine exposure and that fibrosis signaling is downstream to Tgfβ-Smad cascade. Last, we performed an analysis limited to already known thyroid pathways. A few genes were enriched following this method. Specifically, Duoxa1 (hydrogen peroxide generator) and Nis (sodium iodide symporter) were upregulated upon iodine exposure, which are expected responses. Thyroglobulin was decreased and Duoxa1 was increased in Nrf2KO mice confirming our previous findings.
Conclusions
In conclusion, Nrf2-driven cytoprotective response and inflammatory pathways are upregulated after iodine overload. Nrf2 regulates transcriptomic responses in the thyroid, including a small but significant part of the response to iodine challenge. Hence, Nrf2 can be considered a novel player bridging thyroid antioxidant response and thyroid economy.

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YI3

RNA-sequencing of adrenocortical tumors reveals novel pathogenetic insights

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Background
Genetic alterations underlying the pathogenesis of autonomous cortisol secretion and early adrenocortical tumorigenesis have been identified in 40% of adrenocortical tumors (ACT). Nonetheless, the molecular events leading to development of ACT and steroid secretion remain obscure for a large proportion of patients.
Aim
Aims of our study were to investigate the relationship between transcriptome profile and genetic background in a large series of ACT and to identify novel potentially pathogenic molecular event by deep RNA-sequencing.
Methods
We collected snap-frozen tissue from patients with ACT and known genetic background among centers of the European Network for the Study of Adrenal Tumors (ENSAT). Details about somatic mutations were available from previous targeted Sanger sequencing or whole-exome sequencing (WES). We included in the study 52 adenomas (26 associated with Cushing syndrome [CS-CPA], 17 with mild autonomous cortisol secretion [MACS-CPA], and 9 endocrine-inactive, EIA) and 7 early-stage adrenocortical carcinomas (ACC). We performed deep RNA-sequencing for the analysis of gene expression, long non-coding RNA (lncRNA), and gene fusions. We investigated the correlation between RNA-sequencing results and genetic background (i.e. presence of mutations in driver genes - PRKACA, GNAS or CTNNB1, or no mutations in driver genes).
Results
Transcriptome analysis identified two major clusters for adenomas: cluster 1 with EIA and MACS-CPA with CTNNB1 mutations or no drivers and cluster 2 with CS-CPA and MACS-CPA with PRKACA or GNAS mutations and CS-CPA with no drivers. In cluster 2, FATE1 was among most common overexpressed genes. Overall, three CS-CPA with CTNNB1 mutations clustered close to ACC. The analysis of the lncRNA expression showed similar results, confirming the clusters identified in transcriptome profile. ACC showed a higher number of gene fusions per sample (average 8.14) than adenomas (0.79), whereas CTNNB1-CPA had an intermediate number of gene fusions per sample (1.7). We identified novel gene fusions, including an AKAP13-PDE8A fusion in a CS-CPA sample with no previously identified driver mutations.
Conclusions
MACS and EIA showed a similar transcriptome profile, independently of the genetic background. Still unrevealed molecular alterations might be involved in the pathogenesis of adrenocortical tumors associated with cortisol excess. CT

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YI4

Evidence for increased SSTR5 expression and improved pasireotide response in USP8 mutant corticotroph tumours

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The somatostatin analogue pasireotide is approved for the treatment of Cushing's disease, where it achieves biochemical normalization in ~40% of patients. Predicting pasireotide resistance would help avoid unnecessary treatment. Pasireotide mediates its antisecretory action by binding to somatostatin receptor 5 (SSTR5). Almost half of corticotroph tumours carry mutations in the ubiquitin specific protease 8 (*USP8*) gene that encodes for a deubiquitinase. Previous analysis has suggested a correlation between USP8 mutational status and SSTR5 expression. In the present study, we determine the impact of *USP8* mutational status on pasireotide's antisecretory response in vitro and propose a potential mechanism through which USP8 may control *SSTR5* expression. We treated 17 consecutive human corticotroph tumours with 10 nM pasireotide and determined ACTH secretion with a radioimmunoassay, arbitrarily setting physiologically relevant suppression 20% (compared to vehicle control). We assessed 50 archival human corticotroph tumours for *USP8* mutational status by Sanger sequencing and SSTR5 expression by immunohistochemistry (UMB4 rabbit monoclonal antibody). We detected *USP8* mutations in the mutational hotspot of exon 14 in 9/17 (59%) fresh and 21/50 paraffin-embedded corticotroph tumours (42%). Pasireotide treatment suppressed ACTH secretion beyond the 20% cut-off in 11 out of 17 cases (3 *USP8*wt and 8 mutant). We observed more than two-fold inhibitory action in mutant corticotroph tumours (overall % ACTH suppression *USP8*mut 42.6±24.7 vs wt 18.9±10.9; independent *t*-test $P=0.032$). The SSTR5 immunoreactivity score was significantly higher in *USP8* mutant corticotroph tumours compared with wt (mean 0.543±0.338 vs 0,228±0.263, *t*-test $P=0.001$). AtT-20 cells overexpressing the most frequently found in Cushing's disease USP8 mutants p.Pro720Arg, p.Ser-718del and Ser718Pro, showed improved response to pasireotide's inhibitory action on *hPOMC* promoter activity and increased endogenous *Sstr5* -but not *Sstr2*- transcript levels two-fold. The murine *Sstr5* promoter has two binding sites for the activating protein 1 (AP-1). USP8 mutants stimulate AP-1 transcriptional activity, indicating an unexpected mechanism through which activated USP8 regulates SSTR5 levels at transcriptional level. In conclusion, the present study shows that USP8 mutant corticotroph tumours have higher SSTR5 expression and are more prone to respond favourably to the antisecretory action of pasireotide.

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YI5

Splicing machinery is dysregulated in craniopharyngiomas: a novel source of diagnostic, prognostic and therapeutic biomarkers

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Craniopharyngiomas are rare benign epithelial tumors derived from remains of Rathke's pouch. They are more prevalent in childhood, adolescence, and adults <50 years, and, commonly, are usually diagnosed after being associated with serious comorbidities when the development of the tumor is already advanced. To date, first-line therapy is usually surgery, but frequently the resection is not complete, causing high rates of recurrence. Therefore, the identification of new diagnostic and prognostic biomarkers as well as therapeutic tools to improve the management of patient with craniopharyngiomas is necessary. In recent years, a growing evidence indicates that defects in the splicing process are frequent in tumor pathologies, leading to the appearance of altered spliceosome components (SCs), splicing factors (SFs) and/or aberrant splicing variants (SVs; generated by alternative splicing), which are associated to the development, progression and aggressiveness of various cancer types. Based on the information described above, the aim of this study was to establish the expression profile of key splicing machinery components [major and minor spliceosome machinery ($n=13$ and 4, respectively) and 28 relevant SFs] in craniopharyngiomas (primary and recurrent tumors; $n=36$) compared with control samples [normal pituitary glands (NPs, $n=11$)] using a microfluidic qPCR-array, to explore their potential dysregulation and identify specific components of this machinery that could serve as diagnostic and/or prognostic biomarkers as well as therapeutic targets for this pathology. Expression of a substantial number of components of the splicing machinery and SFs were drastically altered in craniopharyngiomas vs NPs, and, also when primary vs recurrent craniopharyngiomas were exclusively compared. Bioinformatic analyses identified RAVER1, RBM22, FBP11 and PRP8 as the most discriminating diagnostic factors of craniopharyngiomas vs NPs. These results were corroborated in two external cohorts (i.e. human and ACP-like mouse model). Furthermore, expression levels of some of these components were associated with key clinical parameters suggesting a potential patho-physiological role of these splicing components in craniopharyngiomas. Finally, the *in vitro* modulation of *RAVER1* and *PRP8* (the most relevant splicing component identified) in primary craniopharyngiomas-derived cell cultures revealed a critical role of these factors in craniopharyngiomas proliferation. Altogether, the expression of key splicing machinery components and associated SFs is dysregulated in craniopharyngiomas, which provides an original approach to identify novel diagnostic and/or prognostic biomarkers and new targets with therapeutic potential in this poorly known disease with multiple endocrine comorbidities.

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YI6

Dysregulation of splicing factor 3B SUBUNIT 1 (SF3B1) is associated with the pathological transformation of the liver: Pharmacological inhibition with pladienolide-B as novel therapeutic tool in liver disease

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Development and progression of liver diseases, from non-alcoholic fatty liver disease (NAFLD) to steatohepatitis (NASH), and hepatocellular carcinoma (HCC), seem to be accompanied by a dysregulation of the expression of alternative splicing variants (SVs) and appearance of aberrant SVs. The splicing factor 3B subunit 1 (SF3B1) represents a crucial player for the functional assembly of the spliceosome, the core machinery that controls the splicing process, and its activity can be specifically blocked using pladienolide-B. Here, we explored the putative dysregulation and pathophysiological role of SF3B1 and the potential therapeutic utility of pladienolide-B in liver disease. To this end, SF3B1 expression (mRNA and protein levels) and clinical implications were assessed in patients with liver diseases from two retrospective ($n=154$ and $n=172$) cohorts, and five *in silico* cohorts of HCC patients [TCGA ($n=369$), Wurmbach ($n=45$), Roessler ($n=43$), Roessler 2 ($n=445$) and Mas ($n=57$)]. Functional and molecular consequences of *SF3B1* silencing (using specific siRNAs) and/or pharmacological blockade (using pladienolide-B) were evaluated in normal-like hepatocyte-derived (THLE-2) and liver cancer (HepG2, Hep3b and SNU-387) cell lines. In addition, Hep3b-induced xenograft tumors treated with pladienolide-B were developed *in vivo*. Results showed that SF3B1 expression levels were consistently elevated (at mRNA and protein levels) in transformed livers (NASH/HCC) compared to normal liver in all cohorts studied. Moreover, *SF3B1* expression levels were associated with clinical (histologic differentiation, overall survival) and molecular parameters of aggressiveness (expression of oncogenic SVs, including KLF6-SV1, BCL-XL, etc). Furthermore, *SF3B1* silencing *in vitro* resulted in reduced proliferation and migration capacity of liver cancer cell lines. Consistently, pladienolide-B

strongly inhibited proliferation, migration, as well as tumorsphere- and colony-formation in liver cancer cells, whereas its effects on the proliferation of normal-like liver cells (THLE-2) were negligible. Remarkably, intratumor injection of pladienolide-B was able to markedly reduce the growth rate of xenograft tumors. Finally, silencing and blockade of SF3B1 both *in vitro* and *in vivo* clearly modulated the expression levels of cancer-associated genes (e.g. *CDK4*, *CD24*) and oncogenic SVs (e.g. *KLF6-SV1*). Altogether, these results demonstrate that SF3B1 expression increases with the pathological transformation of the liver and that its pharmacological inhibition using pladienolide-B may represent a promising novel therapeutic approach worth to be explored through randomized controlled trials, alone or in combination with existing therapies.

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YI7

Congenital isolated follicle-stimulating hormone deficiency due to the FSHB gene mutation in a female patient – a rare case report

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Introduction
Mutations in FSHβ gene leading to isolated follicle-stimulating hormone (FSH) deficiency are very rare and the disorder is inherited in an autosomal recessive manner. Up to date, only few case reports have been described in the literature.
Case report
25-years old woman was admitted to the Endocrinology Department with a suspicion of FSH deficiency. She was firstly diagnosed with primary amenorrhoea and impaired pubertal development at the age of 17. Hormonal tests were performed and low concentrations of FSH and estradiol were found. Pelvic ultrasound and pituitary MRI did not reveal any pathology. Treatment with hormonal replacement therapy was started and continued for 8 years. It was withdrawn 7 days before admission to our department. During hospitalization hormonal function tests were performed and there were found undetectable concentrations of FSH and estradiol, while LH level was mildly elevated. In the gonadotropin-releasing hormone stimulation test there was no response in FSH concentration. Anti-Mullerian hormone (AMH) concentration was within the normal range and inhibin B level was undetectable low. Next-generation sequencing was performed and homozygotic mutation in FSHB gene was found (ENST00000417547c.236-237delTG, protein p.Val79fs). Isolated FSH deficiency was diagnosed.
Conclusion
Hypogonadism and primary amenorrhoea may present a clinical picture of isolated FSH deficiency in women. However, it is worth to notice that a severe deficiency of FSH was not related with AMH deficiency. Patients with isolated deficiency of single gonadotropin give us a new, important insight into its role in human fertility processes, which are still under investigation.

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YI8

Towards the development of an *in vitro* 3D human thyroid model

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Human and animal health has been exposed to endocrine disruptors (EDs) which are chemicals found in pesticides, food or personal care products. The main concern about these disruptors is caused by their interference with the endocrine system causing adverse effects, such as altered reproduction, abnormal neurological development in newborns and children or an elevated susceptibility to hormone-related cancers. The thyroid gland and its hormones belong to major targets that are primarily affected by EDs. Studies on endocrine disrupting effects as well as general endocrine research has been primarily conducted in animal studies due to the lack of representative human models. The importance of the thyroid gland accentuates its role already during embryonic development and organogenesis by secreting thyroid hormones T3 and T4. It further controls the metabolism of various adult organs, the well-being, and the cardiovascular system. The architecture of the characteristic units of the thyroid gland, the thyroid follicles, is a prerequisite for its functionality. A human thyroid test system is urgently needed to evaluate the effects of new substances on endocrine organs. Therefore, the aim of this study was dedicated to advance the field of *in vitro* three dimensional (3D) thyroid research using primary human adult thyrocytes. The hypothesis is based on the importance of a 3D environment and the concomitant cell-cell/cell-matrix interactions to mimic *in vitro* thyroid follicles. In vitro expanded adult thyrocytes, derived from macroscopically normal tissue, were cultured as single 3D culture or in co-culture with endothelial cells (ECs). Adult human thyrocytes dedifferentiated in long-term *in vitro* culture and lost their transcriptional thyroid-phenotype. The results of 3D cultures, independent from the co-culture with another cell type, demonstrate that the 3D environment exerted a beneficial effect on the transcriptional status of thyrocytes by upregulating thyroid-specific markers. It became obvious that 3D culture approaches without supplying additional extracellular matrix were not sufficient to emulate the native thyroid follicle morphology. A reorganization of thyrocytes was finally induced by the co-culture and the addition of Matrigel™. These 3D constructs showed follicular-like structures and are a promising culture strategy for in-vitro test systems of endocrine disruptors. All in all, this study presents for the first time in thyroid research, the successful co-culture of adult human thyrocytes with ECs that induces a reorganization to follicle-like structures *in vitro*.

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YI9

Comparison between the efficacy of the Anti-BAFF monoclonal antibody belimumab vs methylprednisolone in active moderate-severe graves' orbitopathy: an interim analysis

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Background
BAFF is a Serum B cell stimulating factor shown elevated in Graves' disease, compared to controls (Vannucchi 2012). BAFF and its receptor are expressed on lymphocytes infiltrating the thyroid in Graves' disease as well as on thyrocytes themselves (Campi 2015).
Aims
A single-blind randomized controlled trial (EudraCT 2015-002127-26) has been conducted to test the efficacy of the anti-BAFF monoclonal antibody belimumab (BMB) in active moderate-severe Graves' Orbitopathy (GO) compared to iv methylprednisolone (MP).
Methods
We studied the first 20 of the planned 40 patients with active, moderate severe GO and detectable serum TSH receptor antibodies (TRAb), euthyroid for at least 3 months, whether untreated or previously treated with iv steroids (relapsing GO). They received iv belimumab at 0,14, 28 days and then every four weeks for five cycles of infusion or iv MP, 833 mg/ weekly for 6 cycles, followed by one cycle of 425 mg/week. The first dose of belimumab was associated to a full dose (833 mg) of MP. Patient were studied at 12, 24 weeks (primary end point) and followed-up for 48 weeks. In addition to the CAS (primary end point), Gorman diplopia score and proptosis (secondary end points) were also measured.
Results
In both groups CAS decreased significantly at 24 weeks ($P<0.0001$). At 12 weeks patients on MP had a significantly lower CAS than those on BMB (4.8–1.4 vs 4.18–2.45, $P<0.02$). At 24 weeks 9/10 patients had inactive disease (mean CAS with MP 1.33 and with BMB 1.5). No differences were observed in the proptosis and the Gorman score for diplopia with either treatment ($P=$NS). Only one patient (BMB) developed optic neuropathy after the first infusion. In addition, among patients treated with BMB, we

observed one with increased blood pressure, one with headache and dizziness, one with nausea and bile vomiting. Among patients treated with MP, two developed fasting hyperglicemia, one headache, one insomnia, one increased nervousness. Two patients trated with BMB developed epigastralgy, but they were not on pump inhibitor, unlike all patients treated with MP.
Conclusions
The interim analysis suggests that BMB is as effective as iv MP in the treatment of active GO, inducing inactivation in approximately 90% of subjects. Its effect is slower than MP, but its tolerability is very good. If the data is confirmed, BMB is suggested to be a good alternative to MP. Finally, the side-effects profile of BMB is better than MP.

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YI10

Association of dietary and plasma fatty acids with adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) gene expression in human adipose tissues

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Adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) are key enzymes involved in intracellular degradation of triacylglycerols. The environmental factors and circulating biomarkers can affect the expression of ATGL and HSL in adipocytes among rats. To our knowledge, however, no information is known about the dietary and plasma fatty acids composition on gene expression of ATGL and HSL in human adipose tissue. We aimed to determine how fatty acid species measured in plasma and dietary intake associate with HSL and ATGL gene expression in subcutaneous and visceral adipose tissues. In this study, 97 participants aged ≥18 years were selected from patients admitted to the hospital for abdominal surgeries. Visceral and subcutaneous adipose tissues were obtained during the operation those with minimal impact on dietary intake. Habitual dietary intake of participants was collected using a valid and reliable food frequency questionnaire (FFQ), from which the intake of fatty acids was quantified. Plasma fatty acids were assessed by gas-liquid chromatography. The gene expressions ATGL and HSL in visceral and subcutaneous adipose tissue were assessed by Real-Time PCR. After adjustment for total energy intake, sex, HOMA-IR, and age, visceral adipose tissue ATGL and HSL gene expression was associated with total fatty acids concentration ($\beta=0.373$, $P=0.032$ and $\beta=0.411$, $P=0.006$, respectively). Furthermore, visceral adipose tissue ATGL and HSL gene expression was significantly associated with plasma PUFAs ($\beta=0.421$, $P=0.002$ and $\beta=0.395$, $P=0.026$, respectively). Moreover, in visceral adipose tissue, HSL mRNA levels had a significant association with dietary PUFA intake ($\beta=0.471$, $P<0.001$). There was no significant association of dietary intake and plasma fatty acids with ATGL and HSL expression in subcutaneous adipose tissue. Expression of adipose tissue ATGL and HSL positively associated with total fatty acids and PUFA concentration in visceral fat. Besides, dietary PUFA has an association with only HSL in visceral fat. It seems that fat quantity along with quality may be most important for modulating visceral adipose tissue ATGL and HSL gene expression.

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YI11

Growth hormone-releasing hormone (GHRH) antagonists increase the sensitivity to radiotherapy in lung cancer cells

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Growth hormone-releasing hormone (GHRH), apart from stimulating GH secretion in the pituitary, exerts many extrapituitary functions, including stimulation of cell proliferation and survival. GHRH and its receptor splice variants (SVs) are expressed in different cancer cell types, where they modulate cell growth. It has been shown that GHRH antagonists exert anticancer activities in a variety of tumors, including malignant pleural mesothelioma and lung cancer, one of the leading causes of cancer death worldwide. Radiotherapy with ionizing radiation (IR) is currently the first-line treatment for advanced stage lung cancer; however, IR is not always resolutive and is often associated with serious side effects. To date, the role of GHRH antagonists in sensitization of lung cancer to IR remains unknown. Thus, we aimed to verify the antitumor effect of last generation GHRH antagonists, MIA-602 and MIA-690, in human A549 non-small cell lung cancer (NSCLC) cells, in combination with IR. We found that, as previously reported, 24 h treatment with MIA-602 and MIA-690 reduced cell survival and growth in A549 cells NSCLC cells. Interestingly, both antagonists potentiated the inhibitory effect of IR (at 2 and 5 Gy) on cell survival and proliferation, and increased IR-induced apoptosis. Furthermore, MIA-602 and MIA-690 enhanced the IR-induced increase in p53 tumor suppressor protein and the inhibition in Bcl-2 antiapoptotic protein. These effects were paralleled by elevation in expression of genes involved in tumor progression (c-Myc, cyclin B1 and cyclin D1/2), angiogenesis [vascular endothelial growth factor (VEGF)], and invasion [(metalloproteases (MMP)-2, MMP-9 and E-cadherin)]. Ongoing experiments will assess the role of GHRH antagonists in human primary lung cancer cells, along with the regulation of pathways involved in DNA repair (Ku70, Ku80 and DNA-dependent protein kinase). Overall, these results suggest that, in addition to the previously reported inhibitory effects in lung cancer, MIA-602 and MIA-690 may enhance the sensitivity to radiotherapy, thereby increasing the IR-induced antitumor response.

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YI12

Identification of transcriptome profiles in paraffin samples using 3' RNA-sequencing for the prognostic assessment of adrenocortical carcinoma

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Background
Adrenocortical cancer (ACC) is an aggressive tumor with heterogeneous prognosis. Previous genomic studies have demonstrated the importance of molecular classification for the prognostic assessment. Among molecular markers, transcriptome profiles "C1A" (steroid and proliferative signature) and "C1B" (immune signature) show the strongest association with outcome. However these markers are determined so far only from frozen tissue samples, since paraffin-induced RNA degradation prevents the determination of transcriptome profiles using standard technologies on paraffin samples. This limitation hampers the integration of such markers in the routine of pathology departments. The aim of this study was to determine transcriptome profiles from paraffin samples, using a dedicated protocol of RNA-sequencing.
Methods
Tumor RNA was extracted both from frozen (Qiagen) and paraffin (Promega) tissues in 48 ACC patients from Cochin hospital. For 5 patients, several samples (2 to 4) from macroscopically different primary tumor regions were analyzed, including 2 with one area presenting a high Weiss score (> 3) like an ACC and another area with a low Weiss score (< 3) like a benign adenoma. Transcriptome was determined using RNA-sequencing of 3'-end transcripts -that are more resistant to RNA degradation- in paraffin samples

(QuantSeq, Lexogen and Illumina). An unsupervised non-negative matrix factorization consensus clustering was performed on the top most variable genes to classify the transcriptome profiles. These transcriptome profiles were then compared with known prognostic expression marker (*BUB1B-PINK1* differential expression assessed by RT-qPCR) obtained from frozen samples. Association between groups was assessed with Fisher's test. Association with overall survival (OS) and disease-free survival (DFS) was tested using log-rank test.

Results

Sufficient quality of RNA-sequencing (>1 000 000 reads, Q30 > 85%) was obtained for 54/55 paraffin samples (98%). Unsupervised clustering identified 2 main subgroups: one (26 patients, 55%) enriched in proliferative genes was characterized as "C1A", and the other (21 patients, 45%) showing immune and inflammatory signature was characterized as "C1B". Transcriptome profiles were strongly associated with *BUB1B-PINK1* marker ($P < 10^{-5}$), DFS (5-year DFS of 45% and 95% in "C1A" and "C1B" subgroups respectively, $P < 10^{-3}$) and OS (5-year OS of 55% and 95% in "C1A" and "C1B" subgroups respectively, $P = 0.007$). Transcriptome-based classification was stable in different tumor regions from the same patient.

Conclusion

The 3' RNA-sequencing protocol successfully classified "C1A" and "C1B" transcriptome profiles and represents a convenient solution for the determination of gene-expression-based prognostic classification from paraffin samples.

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Audio ePoster Presentations

Adrenal and Cardiovascular Endocrinology

AEP1

Residual corticosteroid production in autoimmune addison´s disease

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Background
Previous research show that autoimmune adrenal insufficiency develops gradually over time and inexorably results in a total inability to produce adrenal steroids. However, growing evidence suggest that a few patients preserve some steroid producing capacity.
Aim
To explore the frequency of residual cortisol production and possible clinical consequences in patients with autoimmune Addison´s disease (AAD).
Material and Methods
We performed a two-staged clinical multicenter study. Study subjects submitted a medication-fasting morning blood sample for analysis of adrenocortical steroids by liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Before sampling, patients abstained from cortisone acetate or hydrocortisone and fludrocortisone for at least 18 and 24 hours, respectively. Residual glucocorticoid (GC) production was defined as quantifiable serum cortisol and 11-deoxycortisol, and residual mineralocorticoid (MC) production as quantifiable serum aldosterone and corticosterone. Clinical variables included demographics, replacement therapy, frequency of adrenal crises, clinical biochemistry, and quality of life. Peak cortisol response was evaluated by a standard 250 µg cosyntropin test.
Results
Fifty-eight of 192 patients (30.2%) had residual GC production, more common in men ($n=33$, $P<0.002$) and in shorter disease duration (median 6 [0–44] vs 13 [0–53] years, $P<0.001$). Residual MC production was found in 26 (13.5%) patients and associated with shorter disease duration (median 5.5 [0.5–26.0] vs 13 [0–53] years, $P<0.004$), lower fludrocortisone replacement dosage (median 0.075 [0.050–0.120] vs 0.100 [0.028–0.300] mg, $P<0.005$), and higher plasma renin concentration (median 179 [22–915] vs 47.5 [0.6–658.0] mIE/l, $P<0.001$). None had a normal cosyntropin response, but peak cortisol strongly correlated with unstimulated cortisol ($r=0.753$, $P<0.000$) and plasma ACTH ($r=–0.694$, $P<0.001$). No differences in HRQoL or other clinical parameters were seen.
Conclusion
In patients with AAD one-third have residual production of glucocorticoids, more common in men and patients with shorter disease duration. In the future, these patients could be candidates for regenerative therapy.

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AEP2

Ovarian adrenal rest tumor in congenital adrenal hyperplasia: Is medical treatment the first line option?

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Introduction
Ovarian adrenal rest tumors (OARTs), in contrast with testicular adrenal rest tumors, are very rare. Up to date, 13 cases were reported in the literature; all treated surgically.
Aim
We describe a case of a young female with uncontrolled classical congenital adrenal hyperplasia (CCAH), presenting with bilateral OARTs, successfully treated with steroid replacement.
Methods
Data on clinical history and biochemical work-upwas obtained from medical records.
Case presentation
A 20 years old women presented with severe abdominal pain, vomiting, diarrhea,and fever. She was known to have 21OH-CCAH. As a result of poor compliance, 6 months before her admission hirsutism worsened and amenorrhea, hyperpigmentation,and weakness developed. ACTH levels were 278< pmol/l and 17OHP 91.3 nmol/l. She was admitted for parenteral antibiotics and high dose hydrocortisone treatment. CT revealed bilateral juxta-ovarian masses (6.2×3.6×7.4 cm left and 5×2.2×3.2 cm right) that on MRI were iso-intense in T1 and hypo-intense in T2, with early enhancement and rapid washout. Trans-abdominal US found the same masses with no ovarian torsion. One week of high dose hydrocortisone resulted in significant clinical and laboratory improvement,and a multidisciplinary teem decided to continue conservative management. The patient was discharged with 2 mg dexamethasone per day. One-month later US revealed shrinkage of the masses and dexamethasone dose was decreased to 1 mg/day. At three months from discharge, she has resumed regular menses,and a repeated MRI (Figure 1) revealed the para-ovarian masseshaveshrunk to 2.7×2.4×5 cm on the left and 1.6×1.4×2.3 cm on the right. Dexamethasone levels were decreased to 0.25 mg/day. One year after the diagnosis, the paraovarian masses shrunk to 2.8×1.9×4.3 on the left (down from 4.6×3.3×7 cm) and 2.1×0.9×1.2 on the right (down from 2.5×1.6×3.9) with less contrast enhancement in comparison to previous test possibly due to fibrotic changes of the tissue
Conclusion
OARTs are rare tumors with a poorly known natural history, and surgery has been the first option in the few reported cases. We demonstrate here that medical treatment is a good alternative, leading to significant tumor shrinkage over a short period.

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AEP3

Is there an epithelial to mesenchymal transition (EMT) in adrenocortical tumours?

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Introduction
Adrenocortical carcinoma (ACC) is an aggressive tumour with unsatisfactory treatment options in advanced disease. Activation of epithelial to mesenchymal transition (EMT) has been described as causative of metastatic spread in human cancers. New drugs were developed targeting EMT with a focus on FGF/FGFR signalling. We here asked whether EMT is relevant in ACC.
Methods
We analysed 6 normal adrenal glands (NAG), 40 adrenocortical adenomas (ACA) and 55 ACC. Epithelial and mesenchymal markers were analysed

by IHC. Expression of FGFR1-4 was quantified using RNAscope and qRT-PCR was employed to quantify expression of 92 FGF-FGFR pathway genes. Isoform switching between FGFR isoforms IIIb (epithelial) and IIIc (mesenchymal) was assessed by qRT-PCR.
Results
Surprisingly, all adrenal tissues lacked E-cadherin expression while N-cadherin was present in both normal and neoplastic adrenal tissues but was significantly lower in malignant vs benign tissues (0.88 vs 1.64, $P=0.007$). SLUG had a uniformly high nuclear expression in all adrenal tissues. FGFR2 mRNA was expressed at lower levels in ACC compared to ACA (3.1 vs 5.2 mRNA copies/cell, $P=0.005$) whereas FGFR1 (8.2 vs 1.7, $P=0.0001$) and FGFR4 (5.5 vs 2.1, $P=0.0004$) were significantly higher in ACC. FGF/FGFR pathway analysis confirmed differential FGFR expression and revealed decreased expression of FGF7, FGF17 and mitogen associated protein kinases in tumors compared with NAG. Again surprisingly, all adrenal tissues had higher expression of IIIc vs IIIb isoform for FGFR. A brief comparison between adrenocortical tissues versus known epithelial tumors as well as mesenchymal tumors shows that in terms of the common markers, adrenal tissues are more mesenchymal than epithelial.
Conclusions
Normal but also tumoral adrenocortical tissues exhibit consistent expression of proteins considered to reflect mesenchymal differentiation. However, significant changes in expression of mesenchymal markers suggest their relevance in adrenocortical tumorigenesis and progression. Receptor tyrosine kinases FGFR1 and 4 may be also a suitable treatment target for advanced ACC.

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AEP4

Copy number determination of steroid 21-hydroxylase gene for the genetic testing of congenital adrenal hyperplasia using real-time quantitative PCR

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Congenital adrenal hyperplasia (CAH) is usually caused by the mutations of steroid 21-hydroxylase gene (*CYP21A2*). *CYP21A2* resides in RCCX copy number variation (CNV), and the genomic structure of RCCX CNV creates difficulties in the genetic testing of CAH. An RCCX CNV allele on one chromosome can carry *CYP21A2* in various numbers. Homozygous deletion of complete *CYP21A2* results in most severe form of CAH, whereas an additional and intact *CYP21A2* copy can replace the lost function of the other *CYP21A2* on the same chromosome. Therefore, the copy number determination of *CYP21A2* has got a profound impact in genetic testing of CAH.
The clinical chemistry validation of duplex real-time quantitative polymerase chain reaction (RT-qPCR) based on hydrolysis probes for the determination of *CYP21A2* copy number was performed on 18 genomic DNA samples from European reference population of HapMap project (CEU), 19 samples with good DNA quality and 12 samples with bad DNA quality. The validation of RT-qPCR for steroid 21-hydrosylase pseudogene and the verifications of RT-qPCRs for complement component genes, HERV-K(C4) CNV alleles and RCCX CNV breakpoint region were also achieved. Estimated limit of detection for *CYP21A2* RT-qPCR was lower than measurement concentration by two order of magnitude, and nonspecific PCR product was not detected by melting curve analysis and microcapillary electrophoresis. PCR efficiency was 1.019 ± 0.077, and linearity was $R^2=0.988\pm0.008$. Repeatability was 0.35 CV% and reproducibility was 0.57 CV%. Accuracy was 7.23 ± 4.28% of the *CYP21A2* copy number, however it was 15.15 ± 7.53% in samples with bad DNA quality. Both clinical sensitivity and specificity were 100%, however, a relatively small number of samples was examined ($n=49$). Robustness was not influenced by the smaller changes of PCR conditions, but different instrument and inadequate RT-qPCR reagent could diminish it. The validation and verification of RT-qPCR for the copy number of other genetic elements of RCCX CNV had got some flaws, however, their performance were reasonable.
The validation of RT-qPCR assay for the copy number determination of *CYP21A2* is fitted for the genetic testing of CAH. In case of need, ambiguous finding in *CYP21A2* copy number can be solved by the consideration of the copy numbers of other RCCX CNV elements.

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AEP5

Cytochrome P450 (CYP) 2W1 affect steroid secretion in adrenocortical cell line and tumor tissues

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Background
The human cytochrome P450 (CYP) 2W1 is involved in the metabolism of several endogenous substrates, including lysophospholipids and fatty acids. Using a polyclonal antibody, we previously demonstrated a high CYP2W1 immunoreactivity in adrenocortical tumors, particularly in those secreting steroids. The aim of the study was to better elucidate the relationship between CYP2W1 and steroid secretion in adrenocortical carcinoma (ACC) H295R cell line and in a larger series of ACC tissues associated with different steroid secretion patterns.
Methods
H295R cells were stably transfected in order to achieve CYP2W1 overexpression, which was confirmed both at mRNA and protein levels. Mock-transfected H295R cells were used as controls. Steroid secretion was evaluated by liquid chromatography tandem-mass spectrometry (LC-MS/MS) using a panel of 13 steroids both at baseline (t0) and after 48h of 1 ∝M forskolin treatment (t1). For the immunohistochemistry (IHC) analysis 203 ACC tissue samples were collected, most of which pertained tumors that secreted cortisol and/or aldosterone alone ($n=64$, 31.5%), followed by endocrine inactive tumors ($n=49$, 24.1%), multiple secreting tumors, including cortisol in combination with other steroids ($n=46$, 22.7%), and androgen-secreting ACC ($n=44$, 21.7%). IHC was performed using a new highly specific monoclonal CYP2W1 antibody (sc374426, Santa Cruz). The relationship between cytoplasmic CYP2W1 immunoreactivity, measured by semi-quantitative H-score, and the steroid secretion pattern at the time of diagnosis was evaluated.
Results
In vitro, aldosterone levels were significantly higher in CYP2W1-transfected cells than in controls both at t0 (21.5 ± 9.2 fold change (FC), $P=0.02$) and t1 (18.3 ± 6.8 FC, $P=0.04$). Cortisol was significantly increased at t0 (3.9 ± 1.1 FC, $P=0.01$), whereas cortisone was higher at t1 (2.4 ± 0.6 FC, $P=0.01$). On the contrary, androgen levels were significantly lower in CYP2W1-cells, including DHEA (-2.1 ± 0.9 FC, $P=0.01$ at t0), DHEAS (-4.1 ± 0.1 FC, $P<0.001$ at t0; -2.00 ± 0.0 FC, $P<0.001$ at t1), androstenedione (-3.3 ± 0.1 FC, $P=0.04$ at t0; -3.7 ± 0.1 FC, $P=0.03$ at t1), and DHT (-2.0 ± 0.2 FC, $P=0.02$ at t1). At IHC analysis, the majority of ACC tissues (56.3%) had CYP2W1 immunoreactivity of H-score = 1. Particularly, CYP2W1 staining was lower in androgen-secreting tumors than in multiple-secreting cases ($P=0.003$), whereas a trend to lower immunoreactivity was observed compared to only cortisol- or aldosterone-secreting ones ($P=0.11$). No significant difference was found between inactive and secreting-ACC.
Conclusion
CYP2W1 may induce cortisol and aldosterone secretion and inhibit androgens secretion both in vitro and in ACC tissues. Further experiments investigating the steroidogenic pathway are needed to confirm our results.

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AEP6

Integrated genomics reveals different subgroups of primary bilateral macronodular adrenal hyperplasia (PBMAH)

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Introduction
Primary bilateral macronodular adrenal hyperplasia (PBMAH) are benign adrenocortical disease responsible for benign tumors and cortisol autonomous secretion. There is a broad spectrum of clinical, imaging and hormonal presentations. Aberrant membrane receptor expression is frequent, the most characteristic example being the food dependent Cushing syndrome due to ectopic expression of the GIP receptor (GIP-R). In 20 to 25 % of these patients, inactivating heterozygous germline mutation of *ARCMC5* explains the development of the disease. The aim of this study was to characterize the molecular alterations in PBMAH and to see whether integrated genomics could identify molecular groups explaining this disease heterogeneity.
Methods
Nucleic acids were extracted from macronodules of adrenal frozen tissue collected in the COMETE tumor bank for 36 PBMAH operated patients. 15/36 patients had a germline *ARMC5* mutation. RNA and micro RNA have been sequenced using Illumina technology/Genomic platform, Cochin Institute. We used Illumina HumanCore BeadChips (306,702 SNPs) to analyze copy-number alterations in these samples, and Illumina MethylationEPIC BeadChip array (866,895probes) to profile DNA methylation.
Results
Half of the tumor samples did not show any chromosomal alterations. A copy neutral LOH of 16p (ARMC5 locus) was observed in 6 patients who carried an ARMC5 mutation. Gain at 1q was observed in 5 patients and gain at 9q21.11–9q34.3 (SF1 locus) in 3 patients. Using the 5000 more differentially methylated positions (SD based classification), we identified two clusters including one corresponding to the *ARMC5* mutated PBMAH. Similarly a specific miRNome profile is observed in the *ARCM5* PBMAH. Transcriptome analysis showed two main clusters: one containing the *ARMC5* mutated PBMAH and one with the WT PBMAH. Interestingly two sub-groups with different gene expression profiles were observed in the WT cluster, suggesting molecular heterogeneity in *WT* PBMAH. The GIP-R was over expressed in one of these two sub-group (fold change 5.8, $P = 5.7E-09$) suggesting a specific molecular profile for food-dependent Cushing PBMAH.
Conclusion
This is the first integrated genomic analysis of PBMAH. It demonstrates molecular heterogeneity of this disease. Three molecular classes of PBMAH determined by gene expression profile, methylome and miRNome are identified: one driven by *ARMC5* mutation and one characterized by GIP-R overexpression. The third one needs to be further investigated. This clusterisation will help to better understand PBMAH pathophysiology and to improve its classification.

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AEP7

Investigation of angiotensin II induced gene expression changes in vascular smooth muscle cells

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The angiotensin II (AngII) hormone exerts a number of biological effects through the type 1 angiotensin II receptor (AT1R). One of the main targets of AngII are vascular smooth muscle cells, their stimulation activates many signaling pathways and results in gene expression changes.
Affymetrix Gene Chip experiments were performed to analyze the effects of AngII stimulation on gene expression. For the determinations, aortic thoracic aorta from young male Wistar rats were usedto obtain primary vascular smooth muscle cells (VSMCs).In our experimental set-up more than 200 genes were upregulated in response to AngII stimulation in smooth muscle cells. In our further experiments, we investigated several genes whose transcription were significantly enhanced by AngII in primary VSMCs (DUSP5, DUSP6, DUSP10, Lmcd1, HbEGF, and endothelin). Our aim was to investigate the kinetics of the gene-expression changes, and to reveal the possible signal transduction processes which lead to the altered expression changes after AngII stimulation. The results of the quantitative PCR measurements also confirmed the increased expression of selected genes upon AngII stimulation. Transcription of most genes was largest two hours after AngII stimulation. Based on our results obtained with different inhibitors, several parallel signaling pathways, e.g. MAPK/ERK signaling may play an important role in the observed gene expression changs. We also investigated the role of epidermal growth factor receptor (EGFR) transactivation in AngII-induced gene expression changes. According to our data, EGFR transactivation does not play a significant role in the gene expression changes in response to AngII stimulation, since genetic silencing of EGFR did not significantlyabolish the AngII induced changes. In our experiments with kinase inhibitors, dasatinib, which acts primarily on the soluble tyrosine kinases ABL and Src, significantly inhibited the induced gene expression changes, suggesting that soluble tyrosine kinases may play an important role in AngII-induced long-term cellular responses. Our results suggest that not only one but parallel signal transduction pathways are responsible for the AngII induced gene expression changes and their effects may be synergistic. Our results may provide important data for understanding the molecular background of various cardiovascular diseases and may even identify novel therapeutic targets. This work was supported by the National Research, Development and Innovation Fund (NKFI K116954 and NVKP_16-1-2016-0039).

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AEP8

Structural instability of mutant variants of 21-Hydroxylase

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Congenital adrenal hyperplasia (CAH) summarizes a group of genetic disorders of enzymes involved in cortisol biosynthesis. The most common causes detrimental mutations in the steroidogenic cytochrome P450 enzyme 21-hydroxylase (CYP21A2). Patients are dependent on a lifelong oral cortisol replacement therapy to ensure survival but quality of life is often reduced and co-morbidities are substantially increased. Also, the administered supraphysiological glucocorticoid dosescannot ideally mimic the circadian rhythm and stress adaption of cortisol secretion. Therefore, the goal of our research is to better understand the specific biophysico-chemical pathomechanism of functional 21-hydroxylase deficiency in order to develop new causative therapeutic approaches. In this work, we investigated the structural and stability properties of six clinically relevant mutant variants of CYP21A2 (V282G/L, P31L, D323G, R484Q/W).Structural and thermal stability were assessed by circular dichroism (CD) spectroscopy. Wild type enzyme showed high α-helical content (65% α-helix) as well as mutants at the position 282 (V282G: 60.6 %, V282L: 57.6%).The α-helical organization in other variants (P31L, D323G, R484Q/W) was more disrupted (42 – 48%) in exchange for mainly random coil. Thermal stability of all mutant variants was reduced (Tm: 41.5 – 45.1°C) compared to the WT (Tm: 47.6°C) in temperature dependent CD spectroscopy. Tryptophan fluorescence experiments to assess denaturant stability of mutant variants also showed higher susceptibility to local unfolding (3.42 – 4.30 M urea) at the hydrophobic core compared to WT using urea as denaturant. Furthermore, in UV/Vis spectroscopy at 280 nm and 418 nm we could demonstrate that all mutant variants had a reduced heme incorporation (A418/A280: 0.20 – 0.63) compared to WT (A418/A280: 0.88). Our results show that correct structural folding and stability pose a major problem in specific mutations involved in CAH. Therefore we propose that structural protein instability plays a key role in the pathophysiology of CAH and thus might constitute a novel tailored therapeutic target for the treatment of affected patients.

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AEP9

Persistent transcriptional disruption and histone mark modifications on visceral adipose tissue after remission of hypercortisolism

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Introduction
Chronic hypercortisolemia during Cushing Syndrome (CS) determines significant changes in the plasticity and function of metabolic tissues like visceral adipose tissue (VAT). Persistence of alterations in VAT function after CS remission is under debate, as data of clinical studies is not consistent

due to confounder factors and limited availability of VAT. Animal model of reversible CS presents long-term alterations on VAT after remission. We investigate VAT alterations at transcriptional and epigenetic level during active and after CS remission employing a translational approach in a reversible CS animal model and CS patients.
Methods
VAT was obtained during abdominal laparoscopic interventions from 6 patients with active ACTH-independent CS due to adrenal cortical adenoma and from 12 controls (CTR) with benign non-inflammatory abdominal pathology matched by sex, age, BMI, metabolic and vascular comorbidities. VAT from C57BL/6 mice with active CS induced by chronic oral GC administration (5 weeks) and mice with cured CS (10 weeks after treatment) was compared to that of CTR mice. RNAseq and ChIPseq were used to analyze gene expression profile and histone mark H3K4me3, H3K27me3 and H3K27ac at both time points in the animal model and human VAT. Differentially expressed genes (DESeq2 algorithm, adj. $P<0.1$; fold-change ≥ 1.5) and putative histone marks associations present in patients were compared with those altered during active and cured CS in the animal model.
Results
Transcriptional analysis of mice VAT revealed 464 up and 366 significantly down-regulated genes persistently altered in active CS and after remission. Gene ontology analysis of the disrupted genes at both times resulted in several pathways and biological process including lipid metabolism, circadian rhythm and inflammation. Moreover, the H3K4me3 and H3K27ac peak- associated genes were commonly maintained at both time points and correlated well with alterations present on gene expression. RNAseq of human VAT showed 69 up and 76 significantly down-regulated genes in CS patients compared to CTR from which 14 genes were commonly altered in the animal model at both time points. Overall analysis of human H3K4m3, H3K27ac and H3K27me3 peaks revealed different profiles between CTR and CS patients. Correlation analysis of commonly altered genes and histone marks signature between mice and human is under process.
Conclusion
Chronic hypercortisolism induces persistent transcriptional disruption in mice VAT long term after remission, from which some are commonly altered in patients with active CS. Potential stable histone marks signatures associated to these persistent altered genes are under study.

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AEP10

Cortisol rhythm in patients with adrenal insufficiency switched from conventional glucocorticoids to dual release hydrocortisone: Impact on metabolic profile

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Background
Several evidences suggested that conventional glucocorticoids (CGCs) used as replacement treatment in adrenal insufficiency (AI) are inadequate to mimic physiological cortisol circadian rhythm (CCR), and that CCR disruption, represented by non-physiological pattern of peaks and troughs and elevated evening GC levels, might be responsible for the increased metabolic and, consequently, cardiovascular risk. It has been demonstrated that once daily dual-release-hydrocortisone (DR-HC), which better reproduces physiological CCR, significantly improves metabolic parameters in primary AI (PAI) and secondary AI (SAI) patients.
Aim
The aim of the current study was to evaluate CCR and metabolic profile in PAI and SAI patients switched from CGCs, particularly cortisone acetate and immediate-release hydrocortisone, to DR-HC.
Methods
Thirteen AI patients (7 SAI and 6 PAI, nine females and four males, 20–66 yrs) were enrolled. CCR ($AUC_{0\text{-}24\ hrs}$) was explored by collecting cortisol blood samples at selected time points (0700–1000 h, 1300–1600–1900–2100 h, 0100–0400–0700 h), at baseline (CGCs) and 12 months after switching to DR-HC. Anthropometric and metabolic parameters were evaluated with standard procedures in a fasting status (1900 h) in the entire cohort;glucose and insulin at fasting and during oral glucose tolerance test (OGTT) were evaluated in a subgroup of nine patients; surrogate indexes of insulin sensitivity/resistance, derived from OGTT, were calculated according to homeostasis model assessment-insulin resistance (HOMA-IR) and Insulin Sensitivity Index (ISI) Matsuda.
Results
Cortisol AUC (1900 h–0100 h) was significantly lower with DR-HC than with CGCs ($P=0.033$), and particularly, cortisol levels measured at 1900 h appeared lower with DR-HC than with CGCs ($P=0.042$). After 12 months of treatment, DR-HC induced a significant improvement in waist circumference ($P=0.004$), and a trend to a significant improvement in body mass index ($P=0.07$); in the subgroup of patients evaluated with OGTT, DR-HC induced a significant reduction in fasting insulin levels ($P=0.039$) and a significant increase in $ISI_{0'}$ ($P=0.012$) and $ISI_{120'}$($P=0.027$).However, no significant correlation was found between cortisol secretion pattern and metabolic changes.
Conclusions
The switch from CGCs to DR-HC in AI patients induces a significant decrease of late evening GC overexposure associated with a significant improvement of visceral obesity and insulin sensitivity. Therefore, this change might induce a beneficial effect on cardiovascular risk in AI patients treated with GCs.

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AEP11

Adrenal cortex is responsive to human chorionic gonadotropin stimulation in patients with adrenal incidentalomas

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Introduction
It is well documented that adrenal tumor tissue is responsive to human chorionic gonadotropin (hCG) as well as to luteinizing hormone (LH) with both hormones sharing a similar physiological role and a mutual receptor.
Objective
The objective of our study was to assess the adrenal steroid response to acute, exogenous hCG stimulation in patients with adrenal incidenatalomas (AI) and for the first time, in a healthy control group.
Methods
Our study group consisted of 39 subjects, 34 patients with AI and 5 age matched healthy controls (63.54 ± 6.91 vs 65.8 ± 3.71 years, $P>0.05$). All patients underwent standard AI endocrinological evaluation. The morning after 1mg dexamethasone suppression test (1 mg DST), 10.000 IU hCG was administered intramuscularly to all subjects, starting at 0800 h with measurements of cortisol, dehydroepiandrosterone-sulfate, testosterone and aldosterone every 30 minutes for 3 hours. The partial response to hCG stimulation was considered as a hormone level raise for at least 25% and the full response for at least 50% during the test.
Results
Based on the cortisol level after 1 mg DST, AI patients were divided in two groups: 15 patients withnonfunctional AI (NAI) and 19 patients with (possible) autonomous cortisol secretion ((P)ACS). There was no difference in age nor in sex distribution between the groups. The only hormone which showed response was cortisol in 20 AI patients: 7 with NAI and 13 with (P)ACS. The cortisol response AUC was significantly higher in (P)ACSthen in NAI patients (15075 (9280.5–31224) vs 4134 (3361.5–4894.5), $P<0.001$).In the NAI group, 3 patients had partial and 4 had full cortisol response to hCG stimulation, while in the (P)ACS group, 6 patients had partial and 7 had full cortisol response. Although more patients with (P)ACS had a response in cortisol then patients with NAI (13 vs 7), there was no significant difference inthe frequency of partial or full cortisol response between the two groups. This suggests that both patients with NAI and (P)ACS are responsive to hCG stimulation in comparison to healthy controls who showed no response at all in all of the measured hormones.
Conclusion
Our results imply that hCG contributes to the cortisol secretion in both NAI and patients with (P)ACS but not healthy individuals. Patients with (P)ACS showed significantly higher cortisol response than NAI. These findings suggest a possibility of cortisol secretion modulation or control through a suppression of luteinizing hormone secretion or action in patients with (P)ACS.

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AEP12

Identification of clinical parameters predictive of ARMC5 mutation in a large cohort of primary bilateral macronodular adrenal hyperplasia (PBMAH) patients.

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Introduction

PBMAH is a rare but heterogeneous disease, characterized by multiple benign adrenal macronodules with variable levels of cortisol excess. In 2013, our team discovered germline heterozygous inactivating mutations of *ARMC5*, acting as a tumor suppressor gene. *ARMC5* mutation rate is 50% in patients with PBMAH treated by adrenalectomy for severe hypercortisolism, 80% in familial cases and 20% in sporadic cases according to the current literature. The aim of this study was to identify predictive criteria for *ARMC5* mutation.

Methods

Since 2014, 454 French and European index PBMAH cases have been genotyped for *ARMC5* in Cochin Institute or in the Genetic Department of Cochin Hospital. To date, among these 454 patients, we have reviewed the 264 consecutive index cases referred from five endocrinology French departments belonging to the COMETE network. A retrospective analysis of the clinical, radiological and biological data was done with a central review of the adrenal CT-scans.

Results

Sixty-five out of the 454 index cases (14.3%) present a germline inactivating *ARMC5* mutation. Similarly, 40 (15.2 %) out of the subgroup of the 264 reviewed patients had a germline *ARMC5* mutation. Patients with *ARMC5* mutations have a more severe disease than wild-type patients, in terms of cortisol excess (UFC 1.92 [0.2 −12.1] vs 0.84 [0.08 − 10.1] fold ULN, respectively, $P=0.017$), adrenal morphology (10.8 [2–27] vs 3.4 [1–13] nodules, respectively, $P<0.001$) and complications (87.5 vs 68.3% of patients treated for hypertension, respectively, $P=0.013$). 100% of the mutated patients have bilateral adrenal nodules AND plasma cortisol after dexamethasone 1 mg suppression test above 50 nmol/l, only 61.6% of the non-mutated patients have these two associated criteria. Therefore, the 100% negative predictive value of the association of bilateral nodules and autonomous cortisol secretion allows to exclude *ARMC5* mutation when both are absent. Using more stringent criteria improved the specificity for *ARMC5* mutations : among the mutated patients, 75.9% had at least 4 and 65.5% had at least 6 adrenal nodules, vs 18.0 and 6.8% of wild-type patients respectively, improving the mutation rate to 37.3% and 57.6%, respectively. However by using these criteria some mutated patients would be missed (24.1 and 34.5%, respectively).

Conclusion

Restricting the indication of *ARMC5* sequencing to patients with bilateral adrenal nodules and a cortisol above 50 nmol/l after 1 mg dexamethasone suppression test could avoid useless genotyping in a third of patients, and would allow a cost and time economy and earlier results, without missing any mutated patient.

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AEP13

Prevalence and incidence of atrial fibrillation in a large cohort of adrenal incidentalomas: A long-term retrospective study

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Background

Chronic glucocorticoids excess leads to morphological and functional cardiac alterations, a substrate for arrhythmias. Autonomous cortisol secretion (ACS) from adrenal incidentalomas is a model of chronic endogenous hypercortisolism, leading to severe cardiovascular diseases.

Aim

To investigate prevalence and incidence of atrial fibrillation in a large cohort of patients with adrenal incidentalomas and ACS.

Methods

After excluding pheochromocytoma, primary aldosteronism, Cushing syndrome, congenital adrenal hyperplasia, and adrenal malignancy, we included 632 patients with adrenal incidentalomas evaluated between 1990 and 2018, aged 18-90 years old. Cortisol after 1 mg-dexamethasone suppression test (DST) < or >50 nmol/l defined non-secreting tumors (NS, $n=420$) and ACS ($n=212$), respectively. We evaluated the prevalence of atrial fibrillation at the time of first evaluation for the adrenal mass. We calculated the incidence of atrial fibrillation during a mean follow-up of 8.6 years (range 6 months-23 years), by retrospective data analysis of 357 patients (249 NS, 108 ACS). Contributing factors associated with prevalence and incidence of atrial fibrillation were analyzed by regression models.

Results

The prevalence of atrial fibrillation was higher in patients with ACS (8.5%) than NS (3.1%, $P=0.003$) and the general population (1.7%; $P<0.001$ vs ACS, $P=0.034$ vs NS). The age-adjusted rate ratio was 1.0 for NS and 2.6 for ACS, compared to the general population. Atrial fibrillation was associated with ACS (Odds ratio 2.40; 95% confidence interval [CI] 1.07–5.39; $P=0.035$). The proportion of patients with atrial fibrillation at the end of follow-up was higher in ACS (20.0%) than NS (11.9%; $P=0.026$). Patients with ACS showed a higher risk of incident atrial fibrillation than NS (HR 2.95; 95% CI 1.27–6.86; $P=0.012$). Post-DST cortisol was associated with risk of atrial fibrillation (HR 1.15; 95% CI 1.07–1.24; $P<0.001$).

Conclusion

Patients with adrenal incidentalomas and ACS are at risk of atrial fibrillation. Electrocardiographic monitoring may be recommended during follow-up.

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AEP14

Comparability of steroid hormone measurement among 9 European laboratories using liquid chromatography-tandem mass spectrometry (LC-MS/MS): Impact of the blood derivative and of calibration

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Background
LC-MS/MS is recommended for accurately measuring circulating steroids. However, laboratories using LC-MS/MS adopt various pre-analytical and analytical strategies, and little is known about comparability of results. Whether different blood derivatives impact LC-MS/MS measurements is unclear, and the benefit of unifying the calibration system among laboratories was not tested.
Aim
Comparisons of LC-MS/MS measurements of circulating aldosterone (Al), corticosterone (B), cortisone (E), cortisol (F), 11-deoxycortisol (11S), 17OH-progesterone (17OHP4), androstenedione (A4), testosterone (T) and DHEAS among 9 European centers. Analysis of the impact of different blood specimens. Assessment of potential benefit of unifying the calibration system.
Methods
Thirteen female and 13 male adult patients in fasting state provided blood between 0800–0900 h into gel separator (gel-serum), beads clot-activator (beads-serum) and Li-heparin (plasma) tubes. Each laboratory analyzed two aliquots of 78 total samples according to laboratory specific procedures. Quantitation was obtained using in house, EUM01041 (BSN, Italy) (external set 1) and 6PLUS1 (Chromsystems, Germany) (external set 2) calibrators. Data were analyzed as inter-laboratory CV.
Results
Median (min-max) CV% were: female range-T, 6.2 (3.0–12.5); E, 6.4 (2.9–12.6); male range-T, 7.0 (4.1–10.9); DHEAS, 7.7 (4.3–14.0); B, 10.9 (4.2–26.5); A4, 11.0 (6.5–21.6); F, 13.0 (6.4–27.3); 11S, 13.5 (5.4–39.0); 17OHP4, 13.8 (6.3–34.0) and Al, 14.4 (6.0–24.1). Samples showing CV > 15% were 0.0% for T, E and DHEAS, and 16.7, 43.6 and 44.9% for B, 17OHP4 and Al, respectively, with minimal differences among specimens. When gel-serum, plasma and beads-serum were separately analyzed, cases with CV > 15% were 38.5, 7.7 and 0.0% for A4, 61.5, 30.8 and 26.9% for 11S, and 61.5, 30.8 and 30.8% for F, respectively. When changing in house calibration with external sets 1 and 2, samples showing CV > 15% were 15.4, 3.8 and 6.4% for A4; 16.7, 32.1 and 26.9% for B; 39.7, 38.5 and 73.1% for 11S; 41.0, 0.0 and 0.0% for F; 43.6, 66.7 and 24.4% for 17OHP4; 44.9, 47.4 and 28.2% for Al; and overall < 5% for T, DHEAS and E.
Conclusions
Inter-laboratory variability was good for T, DHEAS and E, moderate for A4 and B, and poor for 11S, Al, 17OHP4 and F. A4, 11S and F variability worsened with the gel-serum specimen. Unifying the calibration system dramatically improved A4 and F, worsened B, and variably impacted 11S, 17OHP4 and Al measurement comparability. Our data suggest that blood derivatives should be carefully evaluated by each procedure. Caution is required when adopting external calibration as it may not result in improving the harmonization of results.

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AEP15

Multiple hormonal deficiency in heart failure with preserved ejection fraction: Prevalence and role in modulation of antioxidant levels and myocardial dysfunction indexes

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In heart failure with reduced ejection fraction, catabolic mechanisms have a strong negative impact on mortality and morbidity. The relationship between anabolic hormonal deficiency and heart failure with preserved ejection fraction (HFpEF) has still been poorly investigated. On the other hand, oxidative stress is recognized as a player in the pathogenesis of HFpEF. Therefore, we performed a cohort study in HFpEF in order to: 1) define the multi-hormonal deficiency prevalence in HFpEF patients; 2) investigate the relationships between hormonal deficiencies and echocardiographic indexes; 3) explore the modulatory activity of anabolic hormones on antioxidant systems.
Methods
84 patients with diagnosis of HFpEF were enrolled in the study. Plasma levels of N-terminal pro- brain natriuretic peptide, fasting glucose, insulin, lipid pattern, insulin-like growth factor-1, dehydroepiandrosterone-sulfate (DHEA-S), total testosterone (T, only in male subjects) were evaluated. Hormonal deficiencies were defined according to T.O.S.C.A. multi-centric study, as previously published[1]. An echocardiographic evaluation was performed. Plasma total antioxidant capacity (TAC) was measured using the system metmyoglobin -H2O2 and the chromogen ABTS, whose radical form is spectroscopically revealed; latency time (LAG) in the appearance of ABTS•is proportional to antioxidants in sample.
Multiple deficiencies were discovered. DHEA-S deficiency in 87% of patients, IGF-1 in 67% of patients, T in 42%. Patients with DHEA-S deficiency showed lower levels of TAC expressed by LAG (mean ± SEM 91.25 ± 9.34 vs 75.22 ± 4.38 sec; $P < 0.05$). No differences between TAC in patients with or without IGF-1 deficiency were found. A trend toward high level of TAC in patients without hormonal deficiencies compared with patients with one or multiple deficiencies was found.
Regarding echocardiographic parameters, Left Atrial and Left Atrial Volume Index were significantly higher in patients with low IGF-1 values (mean ± SEM 90.84 ± 3.86 vs 72.83 ± 3.78 ml; 51.03 ± 2.33 vs 40.56 ± 2.46 ml/m^2, respectively; $P < 0.05$).
Our study showed high prevalence of anabolic deficiencies in HFpEF. DHEA-S seems to influence antioxidant levels; IGF-1 deficiency was associated with alteration in parameters of myocardial structure and dysfunction. These data suggest a role of anabolic hormones in the complex pathophysiological mechanisms of HFpEF and could represent the basis for longitudinal studies and investigations on possible benefits of replacement therapy.
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AEP16

Effects of adrenalectomy on arterial hypertension in patients with adrenal subclinical hypercortisolism: Preliminary results of a randomized clinical trial

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Introduction
The management of patients with adrenal incidentaloma (AI) and possible subclinical hypercortisolism (SH) is debated. This randomized study was aimed to evaluate the effects of adrenalectomy on arterial hypertension (AH).
Methods
We consecutively evaluated 590 AI patients (referred to 3 Italian Centres between 06/2016 and 12/2019). Among these, 134 patients showed a possible SH (i.e. 1 mg DST between 1.8 and 5 µg/dl). Based on the exclusion criteria we enrolled 56 SH patients (42 F). Patients were randomized in two groups: surgery (Group 1, $n = 23$) or conservative follow up (Group 2, $n = 30$) (3 patients withdrew their consent). Presence of AH was evaluated at baseline and at 6–12 months in the two groups.
Results
So far, 23 patients (9 in Group 1 and 14 in Group 2, mean age 65.1 ± 8.2 years, adenoma diameter 3.0 ± 0.65 cm, 1 mgDST 3.0 ± 2.1 µg/dl) have completed the 6 months follow up. At baseline, the main clinical and biochemical characteristics of the two groups were comparable. In particular, 4/9 patients from Group 1 and 11/14 from Group 2 were hypertensive.
After 6 months, in Group 1 AH improved in all 4 hypertensive patients (1 patient stopped therapy, 2 patients passed from a grade 1 AH to an high-normal blood pressure –BP- without therapy changing, and 1 patient maintained adequate BP despite reducing therapy dose). All non-hypertensive patients ($n = 5$) presented steady BP. In Group 2, 4 patients (28%) worsened the BP control (2 hypertensive patients worsened AH grade and 2 not hypertensive patients at baseline became hypertensive). However, 2 patients (14%) passed

from a grade 1 AH to a high-normal BP without therapy modifications. The remaining8 patients maintained a stable BP control.
Currently,15 patients (5 in Group 1 and 10 in Group 2) have completed the 12 months follow up. The patient from Group 1, who improved AH at 6 months, maintained stable BP levels, while among the remaining patients, including the other hypertensive one, BP remained unchanged vs baseline. Among patients from Group 2, 2 hypertensive patients (20%) worsened BP control, 1 patient (10%) ameliorated the BP control thanks to the increase of the AH therapy, whereas the other 5 hypertensive and the 2 non-hypertensive patients remained stable.
Conclusion
These preliminary data suggest that adrenalectomy has a beneficial role on hypertension in SH patients.
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AEP17

A double-blind, randomized, placebo-controlled phase 3 study to assess the efficacy and safety of relacorilant, a selective glucocorticoid receptor modulator, in patients with hypercortisolism due to cortisol-secreting adrenal adenoma(s)/hyperplasia

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Relacorilant is a highly selective glucocorticoid receptor modulator that antagonizes the effects of excess cortisol while showing no significant affinity for the mineralocorticoid and progesterone receptors. In a Phase 2 study in patients with endogenous hypercortisolism, relacorilant demonstrated improvements in glycemic and hypertension control with no treatment-related hypokalemia or antiprogesterone effects. An international, multicenter, Phase 3 clinical trial, using randomized withdrawal after 22 weeks (22 wk) of open-label treatment, is currently underway to evaluate the efficacy and safety of relacorilant in hypercortisolism of various etiologies (GRACE Study: NCT03697109). In this study, evidence of hypercortisolism must be documented through 2 independent biochemical tests and at least 2 clinical signs and symptoms. Here, we introduce GRADIENT, a double-blind, randomized, placebo-controlled Phase 3 study in approximately 130 patients with less-severe hypercortisolism secondary to adrenal adenoma(s) or hyperplasia. Clinical entry criteria for patients 18–80 years old include a radiologically confirmed adrenal lesion, a biochemical diagnosis of autonomous cortisol secretion, and either impaired glucose tolerance/diabetes mellitus (IGT/DM) and/or hypertension. Participants will receive relacorilant (100 mg/day, titrated to 400 mg/day, as tolerated) or placebo over 22 wk. Biochemical criteria for entry into the study include serum cortisol >1.8 µg/dl after dexamethasone suppression testing and low (<15 pg/dl) or suppressed morning ACTH levels. Patients must be stable on their antidiabetic and/or antihypertensive agents for at least 4 weeks prior to the first dose of relacorilant. The primary efficacy endpoints are the mean change in $AUC_{glucose}$ from baseline to 22 wk for the IGT/DM group and mean change in systolic blood pressure (based on ambulatory blood pressure monitoring) for the hypertension group. Secondary endpoints include changes in weight, waist circumference, quality of life, trabecular bone score, and coagulation markers. The safety analysis will be performed for all patients who received at least one dose of study drug. GRADIENT will be the first double-blind, randomized, placebo-controlled study to test if patients with less severe hypercortisolism secondary to cortisol-secreting adrenal adenoma(s) or hyperplasia benefit from medical treatment.

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AEP18

Aetiology, clinical presentation and mortality of Addison's disease in India: A retrospective follow-up study over 14 years

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Background
Autoimmune destruction is the most common aetiology of primary adrenal insufficiency (PAI) in Europe and north America. In contrast, tuberculosis is a common cause of PAI in developing countries. More recently, adrenal histoplasmosis (AH) is being increasingly reported from India
Aims
To study the aetiology, clinical presentation and mortality in adults with PAI who were diagnosed between 2006-2019 and to determine the changes in aetiology since an earlier study conducted between 1991–1999.
Materials and methods
We conducted a retrospective study of 89 patients (age 15–83 years), diagnosed with PAI between 2006– 2019. An infective pathology was suspected if adrenals were enlarged ($n=65$). Adrenal biopsy was performed in 60 patients. AH was diagnosed by demonstrating *Histoplasma* on staining/culture; adrenal tuberculosis (AT) by granulomas, culture/GeneXpert positive for *M. tuberculosis*, or clinical response to anti-tuberculous therapy (ATT); autoimmune aetiology by normal adrenal size, 21-hydroxylase (21-OH) antibody positivity and/or presence of other autoimmune disorders. Patients received anti-fungal/ATT as per guidelines.
Results
Median duration of symptoms prior to presentation was 6 months. Common presentations were anorexia (97%), weight loss (97%), hyperpigmentation (89%), abdominal pain (36%), and fever (48%). Forty-two (47%) patients presented with acute adrenal crisis. The most frequent aetiologies were AH (45%), tuberculosis (19%) and autoimmunity (25%). Forty-five percent of patients with AH were initially misdiagnosed as AT. Patients with AH were similar to those with AT in their clinical presentation, except for shorter duration of symptoms before follow-up. 21-OH antibody was noted almost exclusively in patients with autoimmune aetiology (41%) and only 1/41 (2%) with infective aetiology. Overall mortality was 18%, over follow-up of 38 (range 1–158) months. Mortality was significantly greater among AH (30%), compared with AT (6%) and autoimmune PAI (5%) ($P<0.001$ between 3 groups) patients. As compared with our earlier report of patients seen in 1991-99[1], where AH was not diagnosed in any patient, AH was now the most common aetiology of PAI.
Conclusions
A recent appearance of AH was noted over the last 15 years. AH was difficult to differentiate from AT on clinical features alone. Despite appropriate therapy, patients with AH had a worse prognosis compared to other aetiologies of PAI.
Reference
1. Agarwal *et al*. *Natl Med J India* 2001 **14** 23–5.

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AEP19

Genes mediating cell growth in aldosterone-producing adenomas

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Objective
Aldosterone-producing adenomas (APA) are a major cause of primary aldosteronism. Somatic mutations explain the excess aldosterone production in the majority of patients with APA with mutations in *KCNJ5* encoding a potassium channel the most prevalent in most reported populations. Mechanisms driving cell proliferation are largely undefined.
Design and method
Quantitative transcriptome analysis using RNA-seq was used to identify differentially expressed genes between macro-APAs ($n=9$, diameter ≥30 mm) and micro-APAs ($n=12$, diameter ≤10 mm). Validation of RNA-seq data by TaqMan real-time PCR was performed for 14 genes in a broader cohort of APAs (NMD, no mutation detected, $n=28$; *KCNJ5*-mutated, $n=43$).
Results
Hierarchical cluster analysis of the 500 genes with largest coefficient of variation indicated sample clustering based on genotype (*KCNJ5* or NMD) and APA diameter. Differential expression of 155 and 348 genes was found between micro- and macro-APAs with *KCNJ5* mutations and NMD, respectively. Among the top 5 overrepresented Gene Ontology terms (biological process), cell death was exclusively enriched in NMD micro- vs

NMD macro-APAs. The expression levels of 10 genes were validated with a potential function related to cell growth. Expression of *BEX1* (a reported tumour suppressor) was 2.8-fold down regulated in macro-APAs relative to micro-APAs ($P<0.001$), and a linear negative correlation of *BEX1* expression with APA diameter was observed in NMD APAs ($r=-0.501$, $P=0.007$). A human adrenocortical cell line with stable expression of *BEX1* was established and showed that *BEX1* induced a reduction in cell viability (difference $P<0.01$ from control cells) and an increase in aldosterone production (2.9-fold increase, difference $P<0.0001$ from control cells).
Conclusions
PA display distinct transcriptome profiles according to adenoma diameter and we show a potential dual function for *BEX1* in APA pathophysiology in adrenocortical cell growth and aldosterone production.

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AEP20

Transcriptomic profiling of canine adrenocortical tumors

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Adrenocortical carcinoma (ACC) is an aggressive cancer, with, in its advanced stages, a median 5-year survival rate of less than 15%. ACC is rare in humans, but in dogs the incidence is at least 100 times higher. Because these dogs receive medical care, have an intact immune system, and have inter-individual and intratumoral heterogeneity, the dog is a unique spontaneous animal model to study new treatment options for ACC. However, to determine similarity of canine and human ACCs, a more in-depth analysis is required. We therefore sequenced the whole transcriptome of 36 canine cortisol-secreting adrenocortical tumors. Bulk RNA was sequenced with the CEL-seq method to produce paired-end 75 base long reads, and reads were aligned to the canFam3 reference genome. After quantification, reads were converted to reads per kilobase of transcript per million reads sequenced (RPKM). Statistics included the Log Rank test for survival analysis and the independent t-test for differences between groups. The tumors were previously classified as either low risk of recurrence tumors (LRT; $n=13$) or moderate-high risk of recurrence tumors (MHRT; $n=23$) based on our newly developed histopathological Utrecht score (a canine variant of the Weiss score). However, in principal component analysis, these groups did not cluster apart. Unbiased clustering analysis divided the tumors into two main groups: 1 and 2. Survival analysis showed that group 2 had a significantly shorter estimated median survival time after adrenalectomy (30 ±5 months) than group 1 (74 ± 7 months) ($P<0.0001$). Significantly upregulated genes in group 2 included several genes also known to be upregulated in human ACCs when compared to adrenocortical adenomas, e.g., TOP2A, PTTG1, CDC2, and ASPM. In addition, genes differentially expressed between the groups included genes important in adrenocortical development such as SHH, but also genes not previously linked to adrenocortical development or tumorigenesis such as CCDC33, HK2, and CYP26B1. The results of this study greatly increase our understanding and improve the classification of canine adrenocortical tumors. This brings valuable insight into how comparable canine ACCs are to human ACCs, and for which treatment targets dogs with spontaneous ACC are a suitable animal model. In addition to previously identified factors in adrenocortical tumorigenesis, these results identify new factors that not only improve our understanding of ACC, but could also be targeted therapeutically.

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AEP21

Psychosocial determinants of body acceptance and quality of life in women with congenital adrenal hyperplasia

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Background
Women with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency have a poor Quality of Life (QoL) compared to the general population and are less satisfied with their body appearance. Data indicates that psychosocial determinants such as good professional and general support could be associated with an improved QoL. Since there is only little data available that has been deduced from samples of small size this effect should be further examined.
Methods
Data of 203 women with CAH aged from 15 – 68 was collected as part of the multicenter dsd-LIFE study performed in 14 specialized centres in 6 European countries. To assess psychosocial determinants, we performed an explorative factor analysis including items of the PRO Questionnaire concerning the participants' satisfaction with their treatment and support in childhood and adolescence, as well as in adulthood. We then built multiple regression models to examine the influence of these psychosocial determinants on the participants' body acceptance and QoL, using the Body-image-Scale (BIS) and the WHOQOL-BREF.
Results
The factor analysis revealed two psychosocial factors which were both significant predictors for all four WHO domains of QoL (physical health, psychological health, environment, social relationships). One of these factors contained items describing the participants' satisfaction with care in the last 12 months and was the most important predictor for the QoL domains psychological health, environment and social relationships. The other factor represented satisfaction with care in childhood and adolescence as well as satisfaction with general support in childhood, adolescence and adulthood. Of these two only this factor was a predictor for body acceptance.
Conclusion
These results show that psychosocial factors such as general and family support, or social interactions with professionals have a significant impact on QoL and body acceptance in adult CAH females. This should be taken into account regarding long-term follow up and multimodal therapy.

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AEP22

The study of cell senescence in cortisol-producing adrenocortical adenoma

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Introduction
Aging is associated with the pathogenesis of many endocrinological disorders, especially for functioning adrenocortical disorders. In addition, mitochondria DNA abnormalities have been reported to be correlated with aging through ROS which eventually resulted in cell senescence. We previously reported that cortisol-producing adenomas (CPA) expressed more abundant cell senescent markers including p16 and p21, compared to other hormone-producing adenomas. However, the detailed pathophysiology of cell senescence and its association with histological features (compact and clear cells) in CPAs have remained unknown. Therefore, we analyzed cell senescent markers examined their correlation with clinicopathological factors in CPA including compact and clear cells respectively. *In vitro* study was performed with exposure to cortisol using H295R cell lines to explore the pathogenesis of cell senescence caused in cortisol-producing lesions.
Materials and methods
We immunolocalized p16, p21,p53 and ki67 in 20 CPAs. mtDNA abnormalities were examined in 20 CPAs, 10 adjacent ZF of CPA and 6 non-functional adenoma (NFA). mtDNA deletion was evaluated by nested-PCR, mtDNA copy number was studied by the relative ratio of copy number compared with diploidy of nuclear-coding genes using real-time PCR. *In vitro* study was performed in H295R cell lines with 10 nM hydrocortisone treatment.
Results
mtDNA copy number of CPA and tumoradjacent ZF were significantly lower than that of NFA. On the other hand, 4977bp mtDNA deletion was more frequently detected in CPA (53%) and adjacent ZF (50%) than in NFA (17%) and CPAs with 4977bp mtDNA deletion harbored higher serum cortisol level than those without 4977bp mtDNA deletion. p53 and Ki-67

were significantly higher in clear than compact tumor cells. However, immunoreactivities of CYP11B1, CYP17A1 and p16 as well as mtDNA copy number were significantly higher in compact than in clear tumor cells. *In vitro* study demonstrated that cortisol could increase p53 and p21 mRNA level, resulting in subsequent suppression of CDK4/6 and cell proliferation in H295R cells.
Discussion
We firstly demonstrated that excessive cortisol did induce cellular and mitochondrial senescent phenotype in CPA as the results of lower mtDNA copy number, frequent mtDNA deletion and higher expression of p21. GR could be involved in the regulation of cell senescence and could possibly control the cell cycles in adrenocortical cells. This study also firstly demonstrated that compact tumor cells harbored high hormonal activity but low proliferative ability while clear cells harbored relatively quiescent but relatively high proliferative ability than compact cells resulting in marked biological intratumoral heterogeneityof CPA.

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AEP23

Mortality in patients with adrenal incidentalomas and autonomous cortisol secretion

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Background
Autonomous cortisol secretion (ACS) in patients with adrenal incidentalomas (AI) has been associated with increased mortality in previous small studies. Our aim was to evaluate if ACS is a risk factor for mortality in a large population of patients with AI.
Methods
Consecutive patients examined for adrenal adenomas, found as AI, without catecholamine or aldosterone hypersecretion between 2005 and 2015 were included and followed for up to 14 years (Clinicaltrials.gov, NCT03919734). Patients were grouped according to predefined levels of cortisol after 1-mg dexamethasone suppression test (DST) (< 50, 50–83, 84–138 and >138 nmol/l). Controls matched for sex and age were randomly selected from the general population (3:1 ratio). Mortality data were collected from the National Registry. Mortality rates were adjusted for age, sex and cardiovascular risk factors.
Results
3980 individuals were included, 995 patients and 2985 controls, of which 170 and 429 died (mean follow-up-time 6.9 years). Mortality rates were similar between controls and patients with DST < 50 ($n = 561$) and DST50-83 ($n = 267$), hazard ratio (HR) 0.98 (0.73–1.30) and HR 0.96 (0.70–1.32). Compared to DST < 50, mortality was similar in the DST50–83 group, HR 1.26 (0.86–1.85).
DST84-138 ($n = 105$) and DST > 138 ($n = 62$) had increased mortality both compared to controls, HR 1.80 (1.19–2.74) and HR 4.06 (2.31–7.15) respectively, and to DST < 50, HR 2.13 (1.38–3.29) and HR 2.91 (1.73–4.89) respectively.
Conclusion
In patients with an AI, a cortisol after DST > 83 nmol/l seems to be a clinically significant risk factor for mortality, while a lower value indicates a risk comparable to the general population.

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AEP24

Real life experience of 8 people with adrenal insufficiency using subcutaneous hydrocortisone infusion in continuous and pulsatile regimens recruited through hydrocortisone pump support group

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Real life experience of 8 people with adrenal insufficiency using subcutaneous hydrocortisone infusion in continuous and pulsatile regimens recruited through hydrocortisone pump support group

Background
Subcutaneous hydrocortisone (HC) infusion using continuous (CSHI) and pulsatile (PSHI) regimes are treatment options for adrenal insufficiency. It is an off-labelled treatment in UK for patients with adrenal insufficiency (AI). Both treatment aim to mimic natural body circadian rhythm of cortisol production. Continuous regimes deliver a consistent rate of hydrocortisone using an Insulin Pump, programmed to mimic a circadian rhythm. Pulsatile regimes use a pump developed specifically for hydrocortisone and aim to more closely replicating circadian rhythms by delivering extra hydrocortisone at mealtimes.
We surveyed 8 cohorts via Cortisol Pump UK support group in Facebook to capture their data in the following area:
Quality of Life AddiQoL scores
24 hours infusion doses & type of regimens
HC doses according to body surface area (BSA)
A&E, hospital admission before & after starting on HC pump
Improvement since started on HC pump
Challenges with HC pump.
Survey Monkey conducted in February 2019
Results
Mean age 47 (31–51); All female; Mean AddiQoL score 87.5/120 with 2 primary AI, 2 unknown, 4 secondary AI. 6 on continuous subcutaneous hydrocortisone infusion and 2 on pulsatile subcutaneous hydrocortisone infusion. Mean length of time on infusion 12 months (10 days - 22 months); mean body surface area dose per day 17.425 mg.
Conclusion
Those with daily dose between 20- 25mg has a higher mean AddiQoL score compare to those with a daily dose above 30mg (100/120 vs 80/120).
Mean daily rate per body surface area is higher than previous studies. A&E visits and hospital admissions in this cohort has reduced from 38 visits to 2 visits for the first 6 months or since started on pump.
Larger studies are needed to look of the effects of these 2 regimens.

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AEP25

The glucocorticoid receptor in macrophages protects against inulin resistance and promotes homeothermy

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Insulin resistance and obesity are a global health problem and directly linked to macrophage-driven inflammation of the adipose tissue. Glucocorticoid therapy, used to treat inflammatory conditions, increases adiposity and insulin resistance. It is unknown however, whether anti-inflammatory actions of glucocorticoids at physiological levels can have beneficial effects on adipose tissue inflammation, potentially limiting insulin resistance. Using a macrophage specific deletion of the glucocorticoid receptor (GR), we show that the glucocorticoid signalling in macrophages protects against obesity related insulin resistance. We found that obese mice lacking the glucocorticoid receptor in macrophages have increased adipose tissue inflammation along with a diminished anti-inflammatory polarisation of adipose tissue macrophages. Macrophages deficient for GR show diminished IL-4 signalling which consequently leads to diminished maintenance of body temperature during cold exposure, linking glucocorticoid action in macrophages to homeothermy. Unexpectedly, this was only attributed to limited browning in subcutaneous but not brown adipose tissue. Similarly, loss of macrophage GR reduced inflammation regulated adipose tissue browning, which increases the drop in body temperature during endotoxin shock. Our results demonstrate that glucocorticoids play an important homeostatic role in macrophages during obesity to limit adipose tissue inflammation and promote insulin sensitivity. We also identify a cooperation of glucocorticoid signalling and IL-4 signalling in macrophages to promote alternative activation, in turn assisting in homeothermy.

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AEP26

Genetic alterations and clinical features in 16 brazilian patients with pheochromocytomas and paragangliomas

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Introduction
Pheochromocytomasand paragangliomas are tumors derived from chromaffin cells which result from mutations of at least six different genes as autosomal dominant disorders.
Aim
To evaluate the existence of correlations between genetic alterations and clinical data in 16 patients with pheochromocytomas and/or paragangliomas.
Methods
From 2007 to 2009, 13 patients with pheochromocytoma [3 men, medium age 39 years (14–61)] and 3 with paraganglioma [1 men, medium age 33 years (22–35)] were evaluated from 2007 to 2019 regarding the presence of genetic mutations and possible correlations between the latter and some clinical features. Besides the mutations, tumor size, symptoms and signs present by the time of the diagnosis were studied.
Results
Four patients had pathogenic mutations (SDHB deletion encompassing the promotor and exon 1, C98Y in the SDHB gene, N78S in the VHL gene, and C634R in the RET gene) and one subject had a V90M variant in the TMEM127 gene. Two patients did not present mutations and nine had nonpathogenic mutations. Regarding the presence of clinical features before treatment, there was a predominance of arterial hypertension (75.0%), while the prevalence of tachycardia, abdominal pain and headaches was respectively 12.5%, 12.5% and 6.25%. There was no significant difference between the age of patients with pathogenic mutations and that of the other patients (31.2 vs 38.6 years, $P=0.3952$). Moreover, there were no differences regarding the prevalence of pheochromocytoma ($P=0.2143$) or clinical features (p: hypertension = 0.6346, tachycardia = 0.4583, abdominal pain = 0.5417, headaches = 0.6875), or tumor dimensions ($P=0.4578$) when the two groups were compared. However, the prevalence of paragangliomas was higher in patients with pathogenic mutations ($P=0.0179$).
Conclusion
In patients with pheochromocytoma and paraganglioma, the absence of correlations between pathogenic mutations and clinical features increases the importance of the genetic studies in the determination of treatment and prognosis of these tumors. Furthermore, subjects with germline mutations associated with pheochromocytoma and paraganglioma should undergo lifelong clinical, biochemical and imaging surveillance and their families should receive genetic counseling.

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AEP27

Peritoneal implantation of pheochromocytoma – two cases of pheochromocytomatosis

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Introduction
Peritoneal implantation of benign pheochromocytomas – also known as pheochromocytomatosis – is a rare event caused by tumour rupture during surgical intervention. In our tertiary referral centre, we managed over two hundred patients with adrenal pheochromocytoma in the past 27 years. Now we report on the two cases diagnosed and followed with pheochromocytomatosis.
Case 1.
A 33-year-old man presenting with paroxysmal hypertension and palpitation was diagnosed with a left adrenal pheochromocytoma (60 mm largest diameter). Laparoscopic adrenalectomy was carried out in 2011. Difficulties manipulating the tumour required deliberate fragmentation to insert it into the entrapment bag. Hypertension and vasomotor symptoms resolved after surgery. Five years later, the patient presented with clinical and biochemical recurrence. During a second surgical exploration in 2017, multiple 2-3 mm nodules were found on the peritoneum forming a tumour-like mass in the left hypochondrium. Debulking tumorectomy with distal pancreatectomy and splenectomy were performed. Metanephrine and normetanephrine excretions remained elevated but non-progressive, 3-metoxitiramin excretion is within the reference range. On the most recent 123I-MIBG SPECT-CT, multiple radiotracer uptaking nodules were visualised on the peritoneal surfaces, around the left kidney and on the lower surface of the liver, however, distant metastases were not described. On doxazosin, the patient has rare mild symptoms of catecholamine excess, however; he is normotensive.
Case 2.
A 34-year-old woman presented with hypertension, palpitation, tremor, headaches, and muscle cramps. She had elevated urinary metanephrine, and abdominal MRI showed a 46 mm pheochromocytoma in the left adrenal. Laparoscopic tumour removal was performed in 2006. Upon dissection, both the capsule and the tumour were found to be ruptured. Urinary metanephrines dropped to normal after surgery. Four years after the primary resection, a non-progressive metanephrine excretion wasdetected, while normetanephrine and 3-metoxitiramin excretions were within normal limits. The patient remained asymptomatic for the next nine years; successfully carried out a pregnancy. Repeated CT, MRI and 123I-MIBG imaging showed multiple nodules in the left adrenal bed and on the peritoneal surfaces, considered to be unresectable. Distant metastases were not visualised. Fourteen years after the primary surgery, the patient is normotensive on prazosin monotherapy.
Family history and genetic testing for hereditary pheochromocytoma/paraganglioma syndromes were negative in both cases.
Conclusions
Benign pheochromocytoma may recur because of tumour capsule rupture and local spillage of tumour cells during surgical resection, with subsequent peritoneal dissemination and implantation. Consecutive pheochromocytomatosis can account for difficult diagnostic and therapeutic challenge.

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AEP28

The role of cytotoxic chemotherapy in adjuvant treatment of radically resected adrenocortical carcinoma

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Background
The recent ESE-ENSAT guidelines on adrenocortical carcinoma (ACC) indicated new treatment options for patients with “high risk for recurrence” as one of the major research topics for the field. However, since almost no data were available on the use of cytotoxic drugs in an adjuvant setting, no clear recommendation could be given. Here we report our experience with adjuvant platin-based therapy since 2002 at the University of Würzburg and MD Anderson.
Methods
22 presumably high risk patients (12 female, 10 male, median age 38.5 years) after radical resection (R0 $n=16$, RX $n=4$, R1 $n=2$), ENSAT stage (II $n=9$, III $n=10$, IV $n=3$) and with median Ki67 of 30%, who were treated with adjuvant platin-based chemotherapy (initiated < 3 months after primary surgery) were matched to patients without adjuvant chemotherapy (using the following criteria: ENSAT stage, resection status, Ki-67, other adjuvant therapies, age and cortisol excess). 19 patients in both group have been treated with concomitant mitotane, none with adjuvant radiotherapy. Primary endpoint was recurrence-free survival (RFS), secondary overall-survival (OS).
Results
Twelve of 22 patients with adjuvant platin-based therapy experienced recurrence, whereas this was the case in 20/22 matched controls. Patients with adjuvant chemotherapy had a significant longer median RFS than matched controls (639 vs 336 days; multivariate adjusted HR: 0.33 (95% CI 0.14-0.79; $P=0.012$). At last follow-up, 4 patients in the chemotherapy group and 12 patients in the control group have been died leading to a trend toward improved overall survival (HR 0.39; 0.09-1.55; $P=0.173$). Neither the highest mitotane blood level in the first three months (12.2 mg/l vs 9.6 mg/l;

$P=0,37$) nor the highest mitotane blood level until progress or end of therapy (17.8 mg/l vs 16.3 mg/l; $P=0,67$) were significantly different between the two groups.
Conclusions
Our retrospective cohort study provides first evidence that adjuvant platin-based chemotherapy may lead to a prolonged recurrence-free and overall survival. The retrospective nature and the size of the study are major limitations. A prospective study (like the just started ADIUVO-2 study) is needed to prove the value of adjuvant platin-based therapy.

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AEP29

Treatment outcomes in 198 patients of the portuguese adrenocortical carcinoma register

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Introduction
Adrenocortical carcinoma (ACC) is a rare entity, usually associated with a poor prognosis. There are still many areas of uncertainty regarding its approach.
Methods
A Portuguese ACC register was established in 2020, including information from 24 endocrine centres. Kaplan-Meier was used to calculate overall survival and recurrence; log- rank test to assess survival and progression free survival (PFS) differences between groups; cox-regression analysis to assess predictors of survival and PFS. Alfa level of significance was 0.05.
Results
198 patients (63% female) with a mean age at diagnosis of 51.96±15.1 years old presented with constitutional symptoms in 62.8%, hormonal hypersecretion in 47.2% and incidentally in 31.82%. The mean tumour size was 11.1 cm±5.09 with evidence of adenopathy in 21.8%, local invasion in 41.6% and distant metastasis in 47.9%. Surgery was performed in 88% of patients with negative resection margins in 61.44%. Mean Weiss score was 4.94±1.6 and mean ki67 17.5%.ENSAT staging was: I – 1.6%; II – 30%; III – 20%; IV – 47.9%. Mitotane was used in 71% of patients, adjuvant radiotherapy was employed in 11%, and different modalities of chemotherapy in 19%. During follow-up: 32% remained disease-free; 27% recurred (63% at the adrenal bed, followed by lung and liver metastasis in 37% and 29%) and 42% progressed (the majority in the lungs and liver 56%, followed by the adrenal bed in 30%). One and five-year survival was 72.7 and 35.7%. One and five-year survival was 92.8/59.5% for ENSAT stage 2; 74.5/34.6% for ENSAT stage III and 35.8/9.9% for ENSAT stage IV. One and five-year PFS was, for stage II, 89.5%/56.5%; for stage III, 54.6/31.9%, and for stage IV, 33.0/0%. Patients with incidentally discovered tumours, lower ENSAT stages, R0 surgery, ki67<20%, low-grade tumours, stage IV patients treated with mitotane irrespective of other chemotherapy, and patients treated with radiotherapy had better survival and PFS in univariate analysis ($P<0.05$). Tumour stage III and IV (HR 4.65 and 13.59, $P<0.001$), age at diagnosis (HR 0.25, $P=0.031$) and incidentally discovered tumours (HR 0.44, p=0.034) were the only independent predictors of survival. Adrenal bed radiotherapy showed a trend towards improved survival (HR 0.25, $P=0.061$). Stage IV was the only independent predictor of PFS (HR 18.36, $P<0.001$).
Conclusions
This is the first characterisation of treatment outcomes of the Portuguese ACC population. Overall survival and its predictors are consistent with published literature, except for age, which impact is still uncertain.

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Excess glucocorticoid activity may suppress tumor immune activity in adrenocortical carcinoma

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Introduction
Excess glucocorticoid (GC) activity has been implicated in the pathophysiology of multiple cancer types. For instance, approximately half of adrenocortical carcinoma (ACC) patients exhibit excess GC (GC+). This provides a unique opportunity to study correlates of GC activity, such as a possible suppression of tumor immune response and immune checkpoint inhibitor (ICI) efficacy due to the broad immunosuppressive effects of GC. ACC multi-omics data can be used to identify the molecular consequences of GC activity and assess the rationale for combining relacorilant, a selective glucocorticoid receptor (GR) modulator, with an ICI in GC+ ACC.
Methods
GC status, mRNA expression, DNA mutation, and DNA methylation data from distinct adrenal resections ($n=71$) were accessed via The Cancer Genome Atlas (TCGA). To deconvolute immune cell type abundance, xCell was applied to the mRNA data. Random forest was used to derive gene signatures.
Results
A significant difference in the expression of858 genes was observed between GC- and GC+ ACC cases. In the GC+ cases, KEGG pathway analysis showed higher gene expression of 7 pathways involved in steroid synthesis and secretion, as well as lower expression in 19 pathways, most of which were related to natural killer cells, T-cells, and immune activity. Hypomethylation was primarily observed in the steroid-synthesis pathways. Tumor-infiltrating $CD4^+$ memory ($P=.003$), $CD8^+$ memory ($P<.001$), and NKT-cells ($P=.014$) were depleted, while tumor-associated neutrophils were enriched ($P<.001$). Moreover, higher tumor mutation burden (TMB) was observed in the GC+ cases ($P=.029$). A gene signature predictive of GC status in ACC was derived and applied to other cancer types to identify tumors with GC+-like transcriptional profiles.
Conclusions
By reducing the abundance of immune cells and immune-related transcripts in GC+ ACC, GC may limit response to ICI therapy. Selective GR modulators such as relacorilant may be able to increase immune related transcripts, thus promoting tumor immune response in GC+ ACC and other malignancies with elevated GC activity. This hypothesis will be tested in a Phase 1 trial of relacorilant+ICI.

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Functional ectopic adrenocortical carcinoma; A case report

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Background
Adrenocortical carcinomas (ACC) are rare malignant tumours, with a quoted incidence of 0.7–2.0 cases/million habitants/year, with ectopic ACC being exceptionally rate. Diagnosis is based on clinical and biological assessment supplemented by imaging. Patients commonly present with features secondary to steroid excess, but around 15% of patients are diagnosed incidentally.
Case Report
A 54-year old lady, presented to clinic for assessment of possible polycystic ovarian syndrome (PCOS). The patient gave a few months history of facial hirsutism accompanied by excessive weight gain and new onset hypertension. On further questioning, she had more sinister symptoms including easy bruising, proximal myopathy and insomnia. Initial investigations revealed a 0900 h cortisol of 867 nmol/l, testosterone 6.73 nmol/l, oestradiol of 129 pmol/l, DHEAS 2.50 umol/l, Androstenedione 9 (0.35-2.49) ng/ml,

17-hydroxyprogesterone of 24.8 ng/ml. 0900 h Cortisol post over-night Dexamethasone suppression test was 1482 nmol/l, ACTH was undetectable and 24-hour urinary cortisol >4138 nmol/24 hr (<806.8 nmol/24 hr).An abdominal CT revealed a 6 cm solid and irregular retroperitoneal mass, in the right iliac fossa, that was separate from the kidney. The lesion increased in size from 6.3 cm to 10.3 cm in 4 months. She had a surgical resection and histology revealed an adrenocortical carcinoma, with a Ki-67 score of 25% and 20 mitoses per high power field. On immunohistochemistry, the tumour cells were positive for melanin A, synaptophysin and inhibin. Post-operatively, the patient was given 6 cycles of etoposide, doxorubicin and cisplatin as Mitotane was locally unavailable, however it was agreed that this is initiated if there is evidence of metastatic disease during follow up. 0900 h Cortisol level on Day 3 post-operatively was 20 nmol/l. She was started on Hydrocortisone 20 mg-10 mg-10 mg peri-operatively, which was tailed down and eventually stopped 7 months later, once Synacthen test showed normal cortisol response. The patient has remained well and is under regular surveillance with the most recent imaging showing no evidence of disease recurrence.

Conclusion

Ectopic adrenocortical carcinomas are exquisitely rare tumours and can constitute an exceptional cause of ACTH-independent Cushing's syndrome. Our case highlights such a functional tumour occurring in a very unusual location, secreting cortisol, androgens and other metabolites. Although very rare, it is an important condition to recognise because of the significant and sinister clinical sequalae that may develop.

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AEP32

A rare case of functioning adrenocortical oncocytoma of uncertain malignant potential in a young female diagnosed with type 1 neurofibromatosis

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Background

Adrenocortical oncocytoma is a veryrare adrenal tumor type, usually non-functioning and benign. Neurofibromatosistype 1 (NF1) is an autosomal dominant disease caused by mutations of the NF1 gene encoding neurofibromin, a tumor supressor gene that acts by activating a RAS GTP-ase which negatively regulates RAS activity. NF 1 is usually associated with pheocromocytoma, rarely with adrenal carcinoma, and no association with adrenal oncocytoma has been reported.

Aim

To report a case of a functioning adrenal oncocytoma in a young patient diagnosed with NF1.

Case report

A 22 years-old-female, with a family history of possible NF1 (father with cafe-au-lait spots) presented in July 2019, following the CT diagnosis of a $9.2 \times 9.6 \times 7.3$ cm right adrenal tumor after a pregnancy loss at week 21. The tumor was apparently encapsulated and homogeneous, without evidence of local invasion or lymphadenopathy. Physical examinationrevealed signs of Cushing's syndrome, hirsutism, acne and multiple cafe-au-lait spots, axillary freckles and Lisch nodules on ophtalmological examination. Hormonal assessment revealed: 0800 h cortisolemia=16.84 mg/dl, unsupressed on LDDST (15.27 mg/dl), ACTH=1.91 pg/ml, DHEA-S=1151 ug/dl (18-391), testosterone=2.06 ng/ml (<0.75), while aldosterone/renin ratio and serum metanephrines were normal. A right open adrenalectomy was performed for the suspicion of adrenocortical carcinoma and the patient was started on prednisone replacement for adrenal insufficiency. On microscopical examination, tumor cells were large, polygonal, with eosinophilic granulated cytoplasm, suggestive of oncocytoma. The mitotic activity was low, without evidence of capsular and vascular invasion and large areas of necrosis were present. Immunohistochemical analysis showed positivity for calretinin and inhibin, confirming an adrenocortical origin. Cytokeratin staining was negative, vimentin was positive. Ki-67 index was 10 %. The Lin-Weiss-Bisceglia score was low (2 minor criteria: large size and tumor necrosis), supporting a diagnosis of functioning adrenocortical oncocytoma of uncertain malignant potential. Postoperatively, on glucocorticoid replacement (due to contralateral adrenal suppression), we observed an improvement of signs of hypercortisolism and androgen excess, paralleling the normalisation of androgens and restauration of cortisol diurnal rhythm and normalisation of ACTH. No signs of local recurrence were observed on the 3 months follow-up CT scan.

Conclusion

Functioning adrenocortical oncocytoma has rarely been described and its association with NF1 is novel. Careful monitoring is required for adrenal tumor relapse and for other NF1-associated tumors.

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Adrenocortical cancer mimicking lymphoma on magnetic resonance scan

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Background

Adrenocortical carcinoma (ACC) is a rare cancer that originates from the cortex of the adrenal gland. Although its exact etiology is not clear, it has been found to be associated with some hereditary cancer syndromes. Sometimes patients present with hormonal excess symptoms (virilization, Cushing's syndrome) or local symptoms consistent with an abdominal mass. In ACC, computed tomography (CT) and magnetic resonance imaging (MRI) are preferred imaging modalities for the localization of the tumor, and the determination of metastases. Myelolipoma, Metastases, lymphoma, and pheochromocytoma should be considered in the differential diagnosis of adrenal carcinoma. Herein, we aimed to present a case of ACC that initially mimics lymphoma with clinical and imaging findings.

Case report

A 42-year-old female presented to our outpatient clinic with a 3-month history of fever (38°C), night sweats, malaise, amenorrhea, abdominal pain, proximal muscle weakness, and deepening of the voice. She was receiving antihypertensive medication therapy. Physical examination revealed peripheral lymphadenopathy and central obesity. Abdominal ultrasonography showed a 164×72 mm mass lesion on the paraaortic area. To define the lesion more accurately, we performed abdominal contrast-enhanced MRI which revealed a $200 \times 130 \times 90$ mm conglomerate solid mass with diffusion restriction that mimic bulky lymphadenopathy. On imaging, the appearance of mass was not clearly distinguishable from adrenal glands. Laboratory tests were found to be compatible with Cushing's syndrome (Table-1). Urinary catecholamines levels were found within normal limits. Thoracic and cervical CT was performed and detected 41×34 mm conglomerate lymphadenopathy at the subcarinal and supraclavicular area. An ultrasound-guided percutaneous tru-cut biopsy was performed from the supraclavicular lymph node to confirm the diagnosis. The patient was diagnosed with metastasis of ACC by histopathology and referred for chemotherapy.

Conclusion

Since complete surgical resection is one of the most important factors which prolong survival, it is very important to make an early diagnosis in ACC. When an intra-abdominal mass is detected, a careful examination should be performed to exclude signs and symptoms of pheochromocytoma, hyperaldosteronism, hyperandrogenism, and Cushing's syndrome. ACC should be kept in mind in case of symptoms of Cushing's syndromeand/or virilization.

Table 1 Laboratory analysis of patient at the time of admission

	Values	Reference Ranges
ACTH (pg/ml)	< 5	0-46
Cortisol (mg/dl)	29,95	6,7-22,6
Dehydroepiandrosterone sulfate (µg/dl)	878	60,9-337
Total testosterone (ng/dl)	336	10-75
17-OH Progesterone (ng/ml)	5,57	0,35-2,9
1 mg DST (mg/dl)	33,21	
2 mg DST (mg/dl)	30,05	
24-hour urine free cortisol (µg/24 hour)	389	< 45

ACTH:Adrenocorticotropic hormone, DST:Dexamethasone suppression test

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Cushing's syndrome during pregnancy - case presentation and follow-up.

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Background
Cushing's syndrome is a rare condition in pregnancy, because infertility is one of the main features of this pathology. Association between pregnancy and cortisol excess involves a high rate of mortality and morbidity for mother and fetus. Hypertension, preeclampsia, diabetes, miscarriage, preterm delivery or sudden intrauterine death can occur. We describe a case of a pregnancy in a patient with a history of Cushing's Syndrome, diagnosed during the previous pregnancy.
Case presentation
A 31 years old patient was diagnosed in 2018 with Cushing's syndrome, during the 19th week of pregnancy. Clinical examination revealed weakness, inspiratory dyspnea, high blood pressure, lower limbs bilateral edema, truncal obesity, moon facies, hirsutism, buffalo hump, purple striae; the paraclinical investigations revealed a right adrenal adenoma (30/35/28 mm) on MRI, proteinuria (0,1 g/l/24 hours), hypoalbuminemia (2,4 g/dl), hypokalemia (2,9 mmol/l). Blood pressure ranged between 160-180/100-120 mmHg despite therapy. Hormonal analyses performed confirmed the diagnosis of adrenocorticotropic hormone (ACTH-) independent CS. The obstetrical ultrasound showed a single, live fetus. The patient's condition deteriorated, developing severe preeclampsia with multiple complications, and a medical board took the decision to terminate the pregnancy for mother's interest. Three weeks later, she underwent laparoscopical right adrenalectomy followed by hydrocortisone replacement.
Results
Evolution was favourable. Her current status in January 2020 reveals regression of all cushingoid features; blood pressure was 110/60 mmHg. Hormonal analyses revealed a normal level for morning serum cortisol (5.74 mg/dl). At the moment, the patient is 26 weeks pregnant, with a good evolution, a single, live fetus, with normal growth and anatomy, according to gestational age and a normal placenta. Her clinical and paraclinical profiles are closely monitored.
Discussion
The serum cortisol increases normally during pregnancy and the screening for Cushing's syndrome is more difficult, particularly in the second and third trimester. The management for such cases is complex and sometimes difficult, especially when a termination of pregnancy is necessary due to severe complication. It requires multdiciplinary approach, with quickly implemented measures. Fertility and overall wellness of the patient could and should be fully reobtained, like in this case.
Conclusion
Pregnancy in a patient with Cushing syndrome induces multiple complications, requiring sometimes termination of pregnancy for mother's interest. Surgical treatment of Cushing syndrome restores the fertility and allows a normal evolution of upcoming pregnancies for such patients.
Keywords: Cushing's syndrome, pregnancy, preeclampsia, laparoscopical adrenalectomy, fertility.
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AEP35

A rare presentation of salt wasting in congenital adrenal hyperplasia with 11β-hydroxylase deficiency.

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Introduction
Steroid 11β-hydroxylase deficiency (11-OHD) is the second most common causeof congenital adrenal hyperplasia (CAH),characterized by the overproduction of adrenal androgens and deoxycorticosterone (DOC).It usually presents with virilization of the female fetus, precocious puberty in male infants and hypertension with or without hypokalemia in both genders. Because of high levels of mineralocorticoids, patients rarely present with salt wasting (SW). We herein report a case of a patient with 11-OHD presenting with SW adrenal crisis.
Case report
A 10-year-old male was admitted to our department for the management of acute adrenal insufficiency. He was born at term to healthy consanguineous parents and had a history of severe dehydration, hyponatremia and sexual ambiguity at birth which was initially diagnosed as 21-hydroxylase deficiency. He was raised as a male but had absent testicles since birth. The patient was irregularly followed up. At the age of 4 years, precocious puberty and arterial hypertension were discovered. At the age of 10 years, the patient was admitted for management of acute adrenal insufficiency due to an abrupt withdrawal of hydrocortisone. On physical examination, he had a body weight of 37 kg (± 2 s.d.), a body height of 1.42 m (± 2 s.d.), a blood pressure of 130/60 mmHg, a masculine morphotype, a sexual ambiquity stage V of Prader and a pubertal development S4 P3 of Tanner. Laboratory examination revealed hypokaliemia of 2.1 mmol/l, normal LH, and FSH levels and high levels of testosterone, 17-OH-progesterone, 11-deoxycortisol, 11-deoxycorticosterone and DHEA-S. Basal 11-deoxycortisol and cortisol levels were 29.6 µg/l [nr: 0.2–1.4] and 0.9 µg/dl respectively and raised to 31.4 µg/l and 1.2 µg/dl at 60th minute, respectively, after ACTH stimulation test. Chromosome analysis revealed a 46XX karyotype. Pelvic ultrasonography showed normal uterine cavity with two ovaries. He was diagnosed as congenital adrenal hyperplasia due to 11-OHD and treated with hydrocortisone and spironolactone. After psychiatric expertise, phenotypic sex was chosen and the patient underwent surgical reparation at the age of 16 years.
Conclusion
Salt wasting crisis is rare in patients with 11-OHD. In newborns, there is a resistance to mineralocorticoids which could contribute to moderate and transient salt loss. However, the combination of both 21-hydroxylase and 11 β-hydoxylase has been reported in literature and it is unclear whether such association is due to a random occurrence of two different mutations or to a single mutation.

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AEP36

Identification of the genetic signature of vascular calcification in patients with type 2 diabetes mellitus by a computational approach

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Introduction
The analysis of the signaling pathways involved in vascular calcification is difficult due largely to the limitation in obtaining vascular tissue samples. Therefore, the use of bioinformatics tools for the identification of potential biomarkers associated with vascular calcification is an advantage for the advancement in the knowledge of the molecular pathways involved in this pathology.
Objective
Increase understanding of the molecular mechanisms involved in vascular calcification processes and to identify potential molecular targets for diagnostic and therapeutic use through the use of bioinformatic resources.
Methods
Calcified femoral artery sections from 7 patients diagnosed with type 2 diabetes mellitus and critical ischemia were used for the study of the proteome by liquid chromatography and mass spectrometry. The set of identified proteins was faced with the set of proteins of 19 similar vascular pathologies described in other studies. In this way, a biological network of proteins associated with vascular calcification was created. The use of bioinformatic tools such as Cytohubba and String allowed to identify a potential genetic signature on which proteins of high degree of centrality and possible subrogated markers were determined.
Results
751 proteins were identified in the characteristic proteome of calcified femoral artery. Seventy one of themwere common proteinsof similar pathologies. The centrality analysis of the common proteins showed that APOE, HP, CAT, MPO and ACTB proteins had the highest value in the centrality ranking. The study of the protein-protein interaction network determined that HSPD1, HSP90B1, SERPINC1, HADHB and PDIA3 could be potential subrogated markers of vascular calcification.

Conclusions
The identified proteins with involvement in vascular pathologies play an important role in processes related to bone mineralization. Therefore, the study of these proteins could be a therapeutic strategy for the joint treatment of vascular and bone pathologies.

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AEP37

Physiologically based pharmacokinetic modelling to inform dosing in adrenal insufficiency and congenital adrenal hyperplasia

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Background
Replacing physiological cortisol levels is important for the long-term health of patients with adrenal insufficiency and congenital adrenal hyperplasia (CAH). Modified-release formulations of hydrocortisone are one strategy being used to replace the cortisol circadian rhythm in adult patients but there is no data in children. Physiologically based pharmacokinetic (PBPK) modelling is a valuable tool for paediatric drug development[1]; however, there are no examples of PBPK simulations for hormone replacement.
Objective
To develop a PBPK model for hydrocortisone.
Methodology
The PBPK model was developed using the Simcyp Simulator population-based PBPK software (Certara UK Ltd., UK; version 16.1). The model includes systems information to account for non-linear binding to cortisol binding protein, metabolism by 11β-HSD2 and 5α-reductase, and how these parameters develop with age. The model was developed and verified using published literature and cortisol pharmacokinetic data measured by LC-MS/MS in healthy adults and adults and children with CAH in trials of an immediate release formulation of hydrocortisone granules (Alkindi, Diurnal Ltd, UK) and a modified-release formulation of hydrocortisone (Chronocort, Diurnal Ltd, UK).
Results
The model predicted immediate-release hydrocortisone PK in adults across the dose range 0.5 to 20 mg, with predicted/observed AUCs within 0.8 to 1.25-fold – defined as a good prediction of the observed FDA bioequivalence criteria based on ± 20% difference - for both the published literature and test cohorts. The model predicted pharmacokinetic parameters for the modified-release formulation, with AUCs within 0.8 to 1.25-fold after single and multiple (representing an 8-hour interval between doses) dosing. After calculation of mg/kg and mg/m^2 modified-release doses roughly equivalent to 20 mg and 10 mg in adults, simulations were performed in a virtual paediatric population aged 12 to 18 years and results compared to equivalent doses simulated in adults. The results showed minimal difference in C_{max}, T_{max}, and AUCs between adults and adolescents.
Discussion
The PBPK model predicted PK parameters in adults and children acrosshydrocortisone dose ranges 0.5 to 20mg and captured the adult modified-release data after single and multiple dosing. Predictions in adolescents aged 12 to 18-years were aligned with current guidelines which recommend hydrocortisone dosing for adolescents with CAH of 10–15 mg/m^2 per day[2]. This PBPK model will provide an invaluable tool in refining dosing regimens for patients who require hydrocortisone replacement therapy and allow prediction of dose for different populations and age groups.
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AEP38

An unusual case of Cushing's syndrome secondary to ACTH producing prostate adenocarcinoma

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Introduction
Cushing's syndrome (CS) secondary to ectopic adrenocorticotrophic hormone (ACTH)–producing prostate cancer is rare with less than 30 cases reported. We report a case of Cushing's syndrome secondary to prostate adenocarcinoma with recurrent hypokalemia, sepsis and rapid disease progression. A 61-year-old man presented in January 2019 with 3-week history of lower limb swelling and weakness. Past medical history is significant for metastatic prostate cancer diagnosed in December 2018 for which he was started on gonadotropin-releasing hormone (GnRH) analogue. His other co-morbidities include hypertension and diabetes. On examination, he had ecchymoses of the upper limbs and proximal myopathy but no other features of Cushing's syndrome. Blood investigations showed hypokalemia with metabolic alkalosis (potassium 2.5 mmol/l, bicarbonate 36 mmol/l) and 0800 h cortisol of 1229 nmol/l. Cushing's syndrome was diagnosed after cortisol failed to suppress after a 1 mg overnight dexamethasone suppression test (cortisol 1327 nmol/l), and 48-hour 2 mg dexamethasone suppression test (cortisol 1447 nmol/l). This was likely to be ACTH-dependent as ACTH was 57.4 (normal range NR 10 – 60) ng/l and high dose 8mg dexamethasone did not suppress cortisol to less than 50% of baseline (cortisol 1424 nmol/l). His 24-hour urine free cortisol was 20475 (NR 59-413) nmol/day. MRI pituitary did not show any pituitary mass. 68Ga-DOTA-NOC PET-CT scan revealed an area of increased DOTA-NOC-avidity in the inferior aspect of the right side of the prostate gland. Review of his prostate biopsy done in December 2018 showed adenocarcinoma with no features of small cell carcinoma, but immunostaining positive for synaptophysin, CD 56 and ACTH. He was initiated on potassium replacement, ketoconazole and spironolactone with improvement of hypokalemia, blood pressure and glucose. Ketoconazole was switched to somatostatin analogue octreotide in view of progressive liver dysfunction. He eventually succumbed to by parainfluenza, varicella and bacterial bronchopneumonia with septic shock, 2 months after diagnsosis.
Conclusion
Adenocarcinoma of the prostate with neuroendocrine differentiation is a rare cause of ectopic Cushing syndrome. It is imperative to recognize and treat ectopic Cushing's syndrome as it has an aggressive course with poor prognosis and limited treatment options.

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AEP39

Effects of endogenous hypercortisolism on selected Angio-miRs expression in humans

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Background and Aims
Higher cortisol levels are associated with cardiovascular mortality in the elderly resulting from potential angiostatic effects of glucocorticoids (GCs). These features are replicated in patients with endogenous GCs excess (Cushing's syndrome) as well as with exogenous hypercortisolism due to excessive pharmacological GCs usage. Both groups present the augmented cardiovascular disease event rate. GCs may also adversely influence remodeling after myocardial infarction via inhibition of angiogenesis. Despite new advances in our understanding of GCs pathophysiology over the past decades, the mechanisms that account for glucocorticoid-related control of vessel generation remain a subject of investigation. Recently, it was proposed that microRNAs (miRNAs), the small noncoding RNAs functioning as antisense regulators of gene expression by targeting mRNA, may have a central role in regulating endothelial function through multiple mechanisms. Thus, the purpose of this study was to evaluate the effects of chronic GC excess on the expression of selected angiogenesis-related miRNAs, called Angio-miRs, expressed in nucleated cells circulating in peripheral blood (PBNCs) of patients with endogenous hypercortisolism either due to corticotrophin-dependent or corticotrophin-independent Cushing's syndrome (CS).

Material and methods
Cells were isolated from circulating peripheral blood collected from 35 healthy subjects and 31 patients with endogenous hypercortisolism as a source of miRNAs. A self-validated individual quantitative RT-PCR study was then performed to evaluate the expression levels of selected Angio-miRs in isolated cells. Additionally, using Western blot technique, the endothelin-1 (ET-1) expression in plasma of peripheral blood was assessed to detect endothelial dysfunction in vasculature.
Results
The performed analysis of selected Angio-miRs revealed a significantly increased intracellular expression of angiogenesis-related miRNAs in patients with CS, including miRNA-150-5p and miRNA-223-3p transcripts compared with healthy subjects. To the contrary, three other potent angiogenic miRNAs, such as miRNA-17-5p, miRNA-126-3p, and miRNA-126-5p, were significantly down-regulated in patients with endogenous hypercortisolism in comparison to healthy volunteers. Besides, the ET-1 expression levels in CS were higher than in healthy subjects, thus, indirectly confirming endothelial dysfunction developed in the CS cohort.
Conclusion
Cardiovascular events related to hypercortisolism remain a challenging problem in clinical endocrinology. This study has demonstrated that the chronic excess of GCs in endogenous CS might induce significant dysregulation of selected Angio-miRs involved in the biologic activity of endothelial cells in peripheral vasculature. Indeed, dysregulated miRNAs seem to be promising targets for further research, especially to search for potential therapies for several GC-induced cardiovascular complications.
Acknowledgements
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AEP40

Association of the subclinical hypercorticism and BclI glucocorticoid receptor polymorphism with bone mineral density in women with adrenal incidentalomas

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Most of adrenal incidentalomas (AI) are nonfunctional, although some of those demonstrate an autonomous subtle cortisol hypersecretion that could lead to increased risk for osteoporosis. Several polymorphisms of glucocorticoid receptor (GR) gene have been found to alter glucocorticoid tissue sensitivity. The aim of this study was toinvestigate whether subclinical hypercortisolism (SH) and *Bcl*I variant of the GR gene have an impact on bone mineral density (BMD) in women with AI. In 106 women with AI, we evaluated BMD with dual-energy X-ray absorptiometry at lumbar spine (LS) and hip. The hypothalamic-pituitary-adrenal axis activity was evaluated using ACTH, midnight cortisol level, 24-h urinary free cortisol, and dexamethasone suppression *tests*. DNA was obtained from peripheral blood leucocytes. The polymorphism was detected using PCR, RFLP and DNA sequencing. Patients with SH had increased frequency of osteoporosis (61.1% vs 22%, $P=0.002$). They had significantly lower BMD at the LS (0.83 ± 0.15 vs 0.93 ± 0.13, $P=0.005$), and total hip (0.79 ± 0.13 vs 0.72 ± 0.11, $P=0.022$). Femoral neck BMD was also lower but the difference did not reach statistical significance (0.66 ± 0.12 vs 0.72 ± 0.11, $P=0.069$). Presence of osteoporosis was associated with SH [odds ratio (OR)=5.775, 95% confidence interval (CI) 1.423-23.426, $P=0.014$] and lower body mass index (OR=1.226, 95% CI 1.071-1.405, $P=0.003$), after adjusting for age, menopause and vitamin-D. Carriers of the C allele of *Bcl*I had significantly less suppression of cortisol levels after 0.5 mg dexametasone (126.4 ± 111.4 vs 80.9 ± 75.7 nmol/l, $P=0.026$). Osteoporosiswas more prevalent in carriers than non-carriers (26.5% vs 7.7%, $P=0.031$). The present study shows that women with AI and SH have higherprevalence of osteoporosis. Although individual bone sensitivity to glucocorticoid is not only influenced by polymorphism, carriers of the longer C allele of *Bcl*I polymorphism exhibit increased sensitivity with enhanced risk of bone density reduction.

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AEP41

Somatostatin receptors 2A and 5 expression in adrenocortical cancer

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Introduction
Adrenocortical carcinoma (ACC) is a rare malignant tumor with heterogeneous prognosis. The median overall survival of all ACC patients is about 3-4 years. Complete surgical resection provides the only cure [Fassnacht M, et al., 2018]. In cases of advanced ACC, therapeutic options are limited. No effective second-line therapies are recommended for patients with disease progression to EDP chemotherapy scheme and Mitotane. It is essential to study alternative drugs, their combinations and tumor biological targets.
Objectives
The aim of the study is to evaluate somatostatin receptor (SSTR) types 2A and 5 expression in ACC.
Materials and methods
Formalin-fixed paraffin-embedded tissues from 69 patients were investigated. All the cases were reviewed according to the Weiss criteria to confirm the presence of ACC. Immunohistochemistry (IHC) staining was performed on 3 μm sections using the Leica Bond Max stainer. The primary antibodies anti-somatostatin receptor types 2A (UMB-1, Epitomics) and 5 (UMB-4, Epitomics) were incubated at the concentration 1:100. Only membranous staining was considered. The IHC results were evaluated through a semi-quantitative approach as negative (0), weak (1+), moderate (2+) or strong (3+) in accordance with intensity of staining. The staining intensity was analysed using the following system: 1+=faint staining at 100× magnification; 2+=strong staining at 100× magnification, not entire circumference of tumor cell membranes stained at 400× magnification; 3+=strong staining at 100× magnification, entire circumference of tumor cell membranes stained at 400× magnification [].
Results and Discussion
We identify moderate or strong staining intensity of SSTR types 2A and/or 5 expression in 49% of ACC spices. The detection of SSTR 2A and/or SSTR 5 expression in tumor tissue may be a promising marker of prolonged somatostatin analogs in the complex therapy of patients with advanced ACC, however, further research is required. There is no ability to evaluate effectiveness of their monotherapy, as well.

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AEP42

Prognostic value of Ki-67 and ENSAT stage on recurrence-free survival and overall survival in patients with adrenocortical carcinoma

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Background
The adrenocortical carcinoma (ACC) is a rare malignancy with poor outcomes and overall survival of less than 40%. Different prognostic factors were evaluated in patients with ACC. We analyzed overall survival (OS) and recurrence-free survival (RFS) in patients with ACC depending on Ki-67 and ENSAT staging.
Methods
We performed a retrospective study on 62 ACC patients treated at the Croatian Referral Center for adrenal gland disorders from 2005 to 2019. Six patients (10%) had ENSAT stage I disease, 30 patients (48%) stage II, 14 patients (23%) stage III and 12 patients (19%) stage IV. RFS was analyzed in 47 patients with the ACC ENSAT stage I-III and R0 resection. Based on Ki-67 patients were stratified in two groups: Ki-67≤10% and Ki-67>10%.
Results
The mean age of patients was 49.1 ± 15.5 years and 70.9% were females. During the study, 15 patients died of whom 10 deaths were related to ACC. The mean OS was 83.3 ± 14.3 months, 153.7 ± 11.3 months, 77.1 ± 14.5 months and 19.7 ± 4.9 months for ENSAT stage I, II, III, and IV, respectively ($P<0.001$). Disease recurrence was observed in 9 patients (19%) of whom two patients had Ki-67≤10%.The mean RFS was 68.3 ± 9.5 months, 109.9 ± 9.4 months and 82.4 ± 16.4 months for ENSAT stage I, II and III, respectively ($P=0.916$). Ki-67>10% was associated with poorer survival ($P=0.04$).

Conclusion
Our data confirmed that the ENSAT stage and Ki-67 are major predictors of ACC patient's survival. However, in our cohort of patients, Ki-67 has not been associated with the ACC recurrence.

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AEP43

CYP11B2 DNA methylation pattern is discordant in aldosterone-producing adenomas and in concurrent aldosterone-producing cell clusters

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Background
Previous studies have shown an association between low CYP11B2 DNA methylation levels and high CYP11B2 mRNA levels in aldosterone-producing adenoma (APA), suggesting that epigenetic mechanisms play a pivotal role for regulating CYP11B2 function in primary aldosteronism. It has been proposed that aldosterone-producing cell clusters (APCCs) may become a source of autonomous aldosterone production when evolving into APA.
Aim
Our aim was to determine whether the CYP11B2 DNA is differentially methylated in APAs and in their concurrent APCCs, and to assess the relationship with CYP11B2 tissue expression.
Methods
A series of 12 formalin-fixed paraffin-embedded (FFPE) adrenal tissues from patients with APA were studied. Immunohistochemical staining was performed using anti-CYP11B1 and anti-CYP11B2 monoclonal antibodies, and anti-CYP17A1 polyclonal antibody. Staining was quantified by the McCarty's H-scoring system. APA, APA-adjacent adrenal cortex, and satellite APCCs identified by immunohistochemistry were microdissected using manual core drilling, and genomic DNA was extracted and assessed for CYP11B2 methylation analysis. CYP11B2 DNA methylation level was measured by quantitative Bisulfite Next Generation Sequencing. Bioinformatic analysis was performed in a GalaxyProject environment and processed by BSPAT (Bisulfite Sequencing Pattern Analysis Tool). The equation 2^-ddCt was used to calculate the fold changes in gene expression between the different intra-adrenal cell structures. Analysis of DNA mutations in aldosterone-driver genes KCNJ5, ATP1A1, ATP2B3 and CACNA1D was performed by Sanger sequencing.
Results
9/12 APA specimens showed at least one concurrent APCC. A wide range of CYP11B2, CYP11B1 and CYP17A1 immunohistochemical expression was detected in tumor cells of APA, while positive CYP11B2 and negative CYP11B1/CYP17A1 staining was uniformly found in APCCs. H-score of CYP11B2 expression in 3/9 APAs was lower than in their satellite APCCs and was generally negative or very low in APA-adjacent adrenal cortex. CYP11B2 DNA methylation levels were significantly lower in APA than in concurrent APCCs and APA-adjacent adrenal cortex ([mean ± standard deviation] 0.51 ± 0.25 vs 0.87 ± 0.11 vs 0.70 ± 0.27; $P < 0.05$ in all but one CpG island considered). Five KCNJ5 and one ATP2B3 mutations were found overall in 12 APAs, including four KCNJ5 and one ATP2B3 mutations among the 9 APAs with concurrent APCCs. No somatic mutations were found in APCCs.
Conclusion
Lower CYP11B2 methylation levels in APA than in concurrent APCCs may sustain the hypothesis of a progressive demethylation process of APCCs, causing their switch to an autonomous aldosterone production. Somatic aldosterone-driver gene mutations do not affect the CYP11B2 DNA methylation rate in APA.

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AEP44

Etiology and extent of impaired quality of life, fatigue and affective, cognitive, and emotional dysfunction in patients with cushing's syndrome – The IQFACE-CS study

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Background
Patients with Cushing's Syndrome (CS) suffer from a variety of neuropsychiatric and cognitive problems. Following remission, some, but not all of these symptoms resolve. Recent cross-sectional studies in patients with CS show persistent structural and functional brain abnormalities. However, longitudinal studies using magnetic resonance imaging, and a detailed neurocognitive assessment, performed before and after treatment, are not available.
Trial objective
To investigate the extent and time-course of restoration of physical and neurocognitive symptoms, as well as functional and structural brain abnormalities in patients with CS.
Methods
The IQFACE-CS study is an investigator-initiated, multicentre, international, prospective observational cohort study (ClinTrial.gov:NCT03211624). Thirty-six patients with active CS and 36 age-, sex-, and education-matched controls will be included. Neurocognitive tests, general and disease specific QoL questionnaires, and functional task-based and structural MRI are performed before treatment and 1 and 2 years after treatment. Currently, 25 patients and 4 controls have been included. Twenty patients were female, mean age at inclusion was 50 years. Ten patients had adrenal Cushing, while 14 had pituitary source. At baseline, mean 24 hour UFC was 723 nmol, mean midnight salivary cortisol was 16.0 nmol/L, and serum cortisol after 1-mg dexamethasone suppression test was 375 nmol/l. Fifteen patients received presurgical treatment with ketoconazole, while 5 patients used metyrapone. Elevated liver enzymes were observed in 5 patients. Mean preoperative 24-hour UFC decreased to 167 nmol. Remission was achieved in 14/17 (82%) operated patients, recurrence was observed in 1 patient during the study period. Four patients have completed the trial.
The study is financially supported by an unrestricted grant fromHRA Pharma.
Conclusion
This study discusses the rationale, design, and progress of the IQFACE-CS study. Inclusion is still ongoing, and final results are expected at the end of 2022.

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AEP45

Regression of the adrenal X-zone controlled by JAK pathway in SF1/SOCS3 KO mice

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Our previous data showed that histological markers of the X-zone in mice adrenal (fetal zone in human adrenal) were still present in adult males and postpartum SF1/SOCS3 KO females. This change led to a distinct distribution of lipid droplets along the adrenal cortex and a blunted ACTH-induced corticosterone secretion in SF1/SOCS3 KO mice. Here we have examined the morphological and functional adrenals of SF1/SOCS3KO male mice adrenals at 3, 8 and 15 weeks through histochemical, immunohistochemical and molecular approaches. The hematoxylin-eosin stains showed retention of X-zone in SF1/SOCS3KO mice adrenals at all ages analyzed. Also, CYP17A1-positive cells were found in X-zone of SF1/SOCS3KO mice. The gene expression analysis by RT-PCR of fetal adrenal enhancer (FAdE) and Pik3c2g genes showed augment, whereas CYP11B1 gene expression was decreased in microdissected X-zone of SF1/Socs3 KO mice adrenals when compared to control male mice, both at 8 weeks age. Taken together, these results showed retention of X-zone in the SOCS3KO mice up to the age of 15 weeks and define the involvement of JAK/STAT/SOCS3 signaling pathway in the X-zone retention and therefore differentiation process of mice adrenal cortex. Supported by FAPESP, CNPq and CAPES.

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AEP46

Fertility testing in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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Introduction
Congenital adrenal hyperplasia (CAH) is an autosomal recessively inherited disorder resulting from the mutations of one of Seven genes involved in adrenal steroidogenesis. The consequent enzyme defects lead to defects of varying severity of steroid biosynthesis. Patients require lifelong substitution treatment and endocrine care.
Objectives
One of the many consequences of CAH is reduced fertility. The aim of this study was to investigate the fertility parameters of 36 patients with 21-hydroxylase deficiency (21-OHD).
Patients and methods
The study included 36 patients (19 women, 17 men) suffering from salt wasting (24) and simple virilizing (12) forms of 21-OHD followed at our endocrine centre. The mean age was 34.5 years (20–48 years). Serum hormone levels essential to follow for optimal treatment were analysed. In males, spermatogram and testicular ultrasound were performed. In women, regularity of menstrual cycles were recorded.
Results
Serum androstenedione (AD) levels were below the lower limit in 5 patients (ref. range: .70-250 ng/dl) while in 2 patients they were above the upper limit of normal. Twenty-four patients had normal serum androstenedione level. Low, normal and elevatedserum 17-hydroxyprogesterone (17-OHP, ref. range: 40-250 ng/dl) concentrations were measured in 2, 13 and 21 patients, resp. ACTH levels were low, normal and increased in 1, 22 and 13 patients, resp. (ref. range: .7.2-63.3 pg/ml). Testicular ultrasound examinations confirmed epididymal cyst in 1 patient, testicular adrenal rest tumors (TART) in 10 patients. Semen analysis was performed in 11 men. Azoospermia, oligozoospermia (<39 million/ejaculations) and normal sperm counts were recorded in four, one and six males, resp. However, considering the sperm concentration (> 15 million/ml), only 4 subjects had adequate results; all of them had satisfactory (> 4%) sperm morphology. Examining the progressive movement of the spermatozoa, reduced movement (asthenozoospermia, less than 32%) was observed in 9 subjects. Overall, considering the number, morphology, and movement of spermatozoa, only 2 (27%) patients had normal values. Among the 19 female patients, 12 underwent feminizing genitoplasty in childhood, and almost all patients still use regular manual vaginal dilation. Nine female patients are using oral contraceptive pills. Four female patients gave birth after spontaneous conception, and two male have children.
Conclusion
Our results confirm that patients with 21-OHD have reduced fertility parameters and conditions in both genders. A multidisciplinary approach including endocrinologist, andrologist and gynecologist is necessary for adequate treatment

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AEP47

Relationship between the hypothalmic-pituitary-adrenocortical axis activity and the characteristics of aldosterone-producing adenomas

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Objective
Aldosterone production can be regulated by adrenocorticotrophic hormone (ACTH) which normally controls cortisol secretion. Some cases of aldosterone-producing adenoma (APA) display features which may suggest increased sensitivity to the stimulatory effects of ACTH. The aim of this study was to investigate if there is any relationship between the hypothalamic-pituitary-adrenocortical (HPA) axis activity and the characteristics of APAs.
Methods
This is a retrospective review of the HPA axis activity of 41 histologically-confirmed APA cases which were characterised with regards to clinical, biochemical and somatic mutation status. HPA axis activity was assessed from morning plasma cortisol, ACTH and 1mg overnight dexamethasone (DEX) suppression test. Correlation was analysed by Pearson's correlation coefficient, and the HPA axis activity between APAs with KCNJ5 mutation and those without was compared using Mann Whitney U-test.
Results
Twelve out of 41 patients (29.3%) were women, median age was 49 years and 85.4% were overweight/obese. All except 2 had somatic mutations within APA. Fourteen (34.1%) were KCNJ5 mutation. Only one patient (APA not KCNJ5 mutated) had post-DEX cortisol > 50 nmol/l. Upright morning plasma aldosterone concentration (PAC) correlated with tumour size ($r=0.347$, $P=0.026$), plasma cortisol ($r=0.425$, $P=0.006$) and plasma ACTH ($r=0.446$; $P=0.056$). Plasma ACTH and cortisol were positively correlated ($r=0.511$, $P=0.025$). Higher PAC, cortisol and ACTH concentrations were in turn associated with the need for higher defined-daily-dose (DDD) of anti-hypertensive medications ($r=0.466$, $P=0.002$ for PAC; $r=0.315$, $P=0.045$ for cortisol; $r=0.449$, $P=0.054$ for ACTH). Higher PAC was also predictive of higher BMI ($r=0.348$, $P=0.026$). Plasma cortisol, ACTH, post-DEX cortisol, BMI and DDD of anti-hypertensives were not significantly different between those with KCNJ5 mutation vs those without.
Conclusions
HPA axis activity correlated with clinico-biochemical characteristics in patients with APAs, but the prevalence of autonomous hypercortisolism was low. The findings suggest a potential role of ACTH in the pathophysiology of APAs. There was no significant difference in HPA axis activity between those with somatic KCNJ5 mutation compared to those without.

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AEP48

Early renin recovery after adrenalectomy in patients with aldosterone-producing adenoma - a longitudinal study.

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Background
Low plasma aldosterone after adrenalectomy due to aldosterone-producing adenoma (APA) and postoperative hypoaldosteronism recovery have been well described. However, prospective time course comparing simultaneously aldosterone and renin levels is still lacking.
Aim
We prospectively studied clinical and biochemical findings emphasizing aldosterone and renin levels, in a cohort of patients with APA who underwent adrenalectomy in a single tertiary center.
Patients and Methods
Of 38 patients diagnosed with primary aldosteronism (PA) from 2016-2019, eighteen patients were diagnosed with APA (11M,7F)and underwent unilateral adrenalectomy. Among them, five were excluded by lost or short follow up, kidney disease, cortisol co-secretion, and aldosterone secreting carcinoma. Blood pressure and antihypertensive requirement as well asserum potassium, aldosterone and direct renin (DRC)concentrations were evaluated before and after 1, 3, 5, 7, 15, 30, 60, 90, 120, 180, 270 and 360 days of adrenalectomy. Aldosterone and DRC postoperative recovery was arbitrary defined as ≥ 5 ng/dl and ≥ 5 mU/l, respectively.
Results
Hypertension was diagnosed at the mean age of 32 years (range 17–52). PA diagnosis was performed with a delay of sixteen years (25–64). The majority of patients had hypokalemia (83%). Post-operatively, median systolic and diastolic blood pressure decreased from 149 to 129 mmHg ($P=0.01$) and

from 91.6 to 81.6 mmHg ($P=0.04$), respectively. Anti-hypertensive daily requirement was decreased and 16% of patients were normotensive with no medications. Median potassium levels increased from 2.8 to 4.7 mmol/l ($P<0.0001$). The median aldosterone and DRC at diagnosis and at last follow up after surgery were 41 vs 5.5 ng/dl and 2 vs 9.1 mU/l ($P<0.0001$).
Renin recovery was observed at median of 15 days (range 3-720) and aldosterone recovery at median of 120 days (5–720). The median difference between renin to aldosterone recovery was 52 days (2–263). In 77% of the patients the renin recovered earlier than aldosterone while in 23% they recoveredsimultaneously. No association was observed between these hormones recovery and age at diagnosis, time of disease, or potassium serum. However, patients with higher aldosterone levels at diagnosis (>41 ng/dl) presented later renin (>15 days; $P=0.03$) and aldosterone (>120 days; $P=0.008$) recovery.
Conclusion
This is the first report, using a prospective protocol, comparing simultaneouslythe short and long-term time-course of aldosterone and renin levels recovery in APA after adrenalectomy. In spite of early renin recovery in most patients, the hypoaldosteronism remained elongated indicating that renin deficiency is not the main cause of postoperative hypoaldosteronism in patients with APA.

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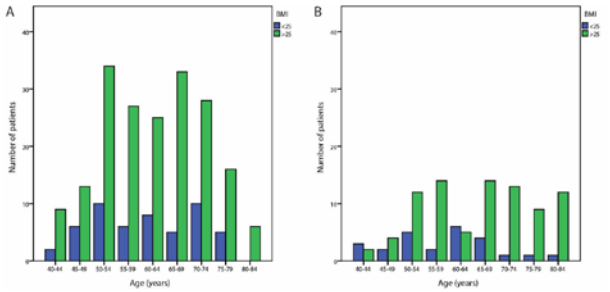

Figure 1 Incidence of AI in NFAI (A) and ACS (B) patients stratified by age and BMI *
*The data analyses for patients below 40 years and above 85 years are truncated because less than 5 subjects were included within those age-subgroups.

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AEP49

Comparison of incidence and characteristics of non-functioning and autonomous cortisol secreting adrenal incidentaloma across different BMI and age distribution

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Background
The relationship between obesity, metabolic traits and adrenal incidentaloma (AI) in clinical studies have been discussed mainly in one direction: as the consequences of mild autonomous cortisol secretion in autonomous cortisol secreting AI (ACS) and as possible consequences of minimal hormonal secretion not detectable by current diagnostic methods in non-functioning (NF) AI. However, the observed anabolic and mitogenic effects of insulin on adrenal cortex from preclinical models led to the hypothesis of the potential existence of bilateral relationship between obesity and AI. In clinical studies, obesity as a primary cause of AI and as a main risk estimator of metabolic burden in patients with AI remained largely unaddressed.
Purpose
We compared the incidence and characteristics of non-functional (NF) and autonomous cortisol secreting (ACS) adrenal incidentaloma (AIs) after cohort was stratified by different body mass indexes (BMI) and age groups.
Methods
Cohort study comprising of 432 patients (40,6% male, 59,4% female) with NFAI ($n=290$) and ACS ($n=142$), of median age 63.4 (54.0–71.6) years and median BMI 28.6 (25.5–31.7) kg/m^2. The data collection contained 11.132 points including demographic, anthropometric, radiologic, hormonal and metabolic parameters.
Results
We observed 68-87% higher incidence of AI across different age groups in NFAI and ACS if BMI was >25 kg/m^2 compared to BMI ≤25 kg/m^2 (Figure1). Patients with ACS were older ($P=0.008$), with higher basal cortisol ($P<0.001$), lower basal DHEAS ($P=0.001$), lower suppression DHEAS ($P=0.027$) and higher aldosterone ($P=0.039$). AIs with ACS were larger than NFAI. Interestingly, ACS group had lower body mass ($P=0.023$) and did not differ in BMI, blood pressure, heart rate, lipid profile, fasting glucose and presence of diabetes mellitus type 2 when compared to NFAI. By contrast, some components of metabolic profile were rather associated with higher BMI and older age, in particular in NFAI.
Conclusion
The incidences of NFAI and ACS were significantly higher in overweight/obese subgroup across the age distribution. Incomplete post-dexamethasone cortisol suppressionwas not a reliable predictor of metabolic alterations, whereas stratification by age and BMI displayed significant differences in some metabolic traits, in particular in NFAI.

AEP50

Prevalence of primary aldosteronism and association with cardiovascular complications in patients with resistant and refractory hypertension

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Background
Primary aldosteronism (PA) is the most frequent form of secondary hypertension, with a high prevalence in resistant hypertension (RH), a condition of insufficient blood pressure (BP) control despite a 3-drug based treatment at full dose, including a diuretic. The prevalence of PAin refractory hypertension (ReH), a condition of persistently elevated BP values despite therapy with 5 drugs, is not known.
Objective
To investigate the prevalence of PA in RH and ReH and its association with cardiometabolic complications, atrial fibrillation (AF) and aortic ectasia.
Subjects and Methods
We enrolled consecutive patients with RHand without previous cardiovascular events, referred to our Center for Hypertension, Division of Endocrinology, Diabetes and Metabolism, University of Turin, between 09/2011 and 09/2019. PA was diagnosed when the following conditions were met: PAC >150 pg/ml, PRA <1 ng/ml per hour, ARR >400 and PAC after SIT >100 pg/ml.
Results
110 patients with RH were enrolled. PA was diagnosed in 32 cases (29.1%). In univariate analysis, PA patients was associated to male gender, hypokalemia, worse hypertensive profile, single and cumulative organ damage (OD) (microalbuminuria, chronic kidney disease, carotid Intima Media Thickness andLeft Ventricular Hypertrophy), aortic ectasia and atrial fibrillation. The multivariate analysis showed that PAis a strong factor associated with left ventricular hypertrophy (OR=13.13, 95% CI 3.79-62.70; $P<0.001$), microalbuminuria (OR=3.77, 95% CI 1.45–10.21; $P=0.007$), carotid intima-media thickness (cIMT)≥0.9 mm (OR=2.81, 95% CI 1.02–8.19; $P=0.049$), aortic ectasia (OR=7.93, 95% CI 2.09–52.36; $P=0.008$) and atrial fibrillation (OR 8.54, 95% CI 1.53–70.77; $P=0.022$). Moreover, PA was independently associated with the presence of at least one type (OR=8.60, 95% CI 1.73–69.88; $P=0.018$) and at least two types of OD (OR=3.08, 95% CI 1.19–8.24; $P=0.022$). 13 patients (11.82%) were affected by ReH. This group was characterized by higher valuesof cIMT (1.20, 1.00–1.40 vs 0.70, 0.60–0.90 mm; $P=0.002$), higher rate of aldosterone producing adenoma (23.08% vs 6.19%; $P=0.041$) and atrial fibrillation (23.08% vs 5.15%; $P<0.049$), if compared to the other subjectswith RH.

Conclusions
The present study indicates that primary aldosteronism is a frequent cause ofsecondary hypertension andcardiovascular complications among patients with resistant andrefractory hypertension, suggesting acrucial role of aldosterone in the pathogenesis of severe hypertensive phenotypes and cardiovascular disease. Physicians should not stigmatize the relevance of an ineffective multiple drug antihypertensive therapy and should refer patients with RH to hypertension reference centers, because specific treatment of PA improves OD and reduces the incidence of cardiometabolic complications.

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AEP51

Isolated acquired hypoaldosteronism as a cause of hypovolemic hyponatremia with urinary sodium loss

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Isolated acquired hypoaldosteronism (HA) is considered to be a cause of hypovolemic hyponatremia (HH) with urinary sodium loss (UNaL) and hyperkalemia/upper-limit serum potassium (SK). However, some authors question the presentation of hyponatremia of these characteristics in the absence of Addison's disease (AD).We present a series of patients with HA.
Methods
Aretrospective study of 70 cases of HH with UNaL (UNa > 25 mmol/l) and SK ≥ 5 mmol/l or in upper limits (≥ 4.8 mmol/l) with inadequately low urinary potassium (UK), in absence of oliguria. Patients were assessed for hyponatremia by the Endocrinology Department of a tertiary hospital, from 2012–2019. All presented a low central venous pressure (indicated by the internal jugular vein pulse). AD was ruled out as follows: basal cortisol > 15 µg/dl, or basal cortisol between 10-15 µg/dl with ACTH < 40 pg/ml or use of pharmacological doses of glucocorticoids (GC) during the episode. Reference aldosterone (RIA) values: 90-200 pg/ml.
Results
44/70 (62.9%) were women, mean age: 75.5 years (SD: 12.7). Mean values at diagnosis:serum Sodium 128.5 mmol/l (SD: 5.80), SK 5.5 mmol/l (SD: 0.4), UK 28.8 mmol/l (SD: 11.3), bicarbonate 21.5 mmol/l (SD: 3.2), trans-tubular potassium gradient 4.2 (SD: 1.2). 66/70 (94.3%) presented hyperkalemia with a mean zenith SK of 5.8 mmol/l (SD: 0.5), 67.9% presented metabolic acidosis (MA) with normal anion GAP, 66% hyperkalemia with MA. Morning serum cortisol was available in 54 cases, mean cortisol without GC: 17.2 µg/dl (SD: 5.2). AD was diagnosed in 3/70 cases (4.3 %), AD was ruled out in 43/70 cases (61.4%). 24/70 cases were "indeterminate", requiring further testing and follow-up, during which no additional cases of AD were diagnosed. In 29/43 patients with AD ruled out, serum aldosterone was measured during the episode, permitting differential diagnosis of HA. 16 cases were secondary to aldosterone deficit, with low aldosterone levels: median aldosterone 52 pg/ml [IQR: 21.5 – 82.5]. 7 cases were due to mineralocorticoid resistance, with elevated aldosterone levels: median aldosterone 258 pg/ml [IQR:223 – 293]. 6 cases presented a combination of aldosterone deficit and resistance, with inadequately "normal" aldosterone levels for hyperkalemia: median aldosterone 153.5 pg/ml [IQR: 129.35 – 177.65].
Conclusion
Isolated acquired hypoaldosteronism, due to aldosterone deficit and/or mineralocorticoid resistance, can induce hypovolemic hyponatremia. Furthermore, it is a more frequent cause of hypovolemic hyponatremia with urinary sodium loss and hyperkalemia than is Addison's Disease, in patients studied for hyponatremia.

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AEP52

Ambulance alert system enabling pre-hospital parenteral steroids for patients with adrenal insufficiency

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Background
For patients in an adrenal crisis, the timely administration of parenteral hydrocortisone can be life-saving. Data from the Addison's Disease Self-Help Group found that a large proportion of adrenal crises occur out of hospital, with many patients relying on the emergency services for initial parenteral hydrocortisone administration. Despite regular patient education (including parenteral hydrocortisone self-administration) and recommendations to wear steroid alert jewellery or carry steroid alert cards, it is not uncommon for patients with primary or secondary adrenal insufficiency to experience delays in the administration of potentially life-saving hydrocortisone injections when unwell often due to health care services being unaware of their diagnosis.
Aim
The aim of this project was to identify the current local rates of emergency attendance of steroid-dependent patients and the rates of pre-hospital parenteral hydrocortisone administration to help guide service-development.
Methods
STHK is a large secondary care hospital in the North West of England with over 800 beds and up to 450 emergency department presentations per day. A list of steroid-dependant patients was obtained from the endocrine outpatient department, and using the hospital electronic records a search was performed on all hospital attendances over the 3-year audit period (2015–2018). Following collection of this data, we worked extensively with our local information governance team and North West Ambulance Service NHS Trust (NWAS) to set up a data-sharing agreement for patients with adrenal insufficiency. Following patient consent, we securely upload patient details to the NWAS Electronic Referral and Information Sharing System (ERISS).
Results and Outcomes
More than 50% of our steroid-dependent patients attended hospital as an emergency within the time period. 78% of patients arriving by ambulance did not receive pre-hospital parenteral hydrocortisone. 56% of patients arriving by ambulance did not receive parenteral hydrocortisone upon attendance to AED. With the ERISS upload and through collaboration with NWAS, following a 999 call, NWAS paramedics and call-handlers are automatically notified that the patient involved requires parenteral hydrocortisone upon emergency service contact.
Conclusions
For patients with adrenal insufficiency, a delay in parenteral hydrocortisone in an emergency can be fatal. A high proportion of steroid-dependent patients within the St Helens and Knowsley region do not receive parenteral hydrocortisone in a timely fashion when becoming significantly unwell. Through an information-sharing arrangement with the ambulance service, we have set up this safety net to ensure that no patient of ours with adrenal insufficiency misses out on this potentially life-saving treatment during an ambulance-callout.

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AEP53

Trends in the incidence of adrenal incidentaloma diagnosed by CT abdomen in 2002 and 2015: Preliminary data from a retrospective study in regional sweden

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Background
Adrenal incidentalomas (AI) are common and reported at frequencies of 2-10% at CT-scans of the abdomen. It is established that the number of diagnosed and investigated cases of AI have increased over the last decades. This increase is closely related to the development of modern radiology. General access of CT scanners with higher performance have led to an improved capacity and consequently more performed investigations. Other contributing factors are improved imaging technique with higher resolution images and other effects that can enhance the possibility to detect adrenal masses. Increased knowledge and attendance of AI among radiologists are other important factors that probably also entail a more structured and clear reporting

of the findings, which increases the likelihood that the diagnosis is recorded and that an adequate investigation is conducted.
Aim
To describe the development of the absolute numbers in relation to frequency of AI diagnosed with CT abdomen 2002 and 2015 in Regional Sweden.
Method
Retrospectively we reviewed all digital imaging reports of CT-scans of the abdomen performed on patients >18 years at four hospitals in Regional Sweden in 2002 and 2015. To identify missed cases, images were reviewed if the adrenals were not mentioned in the report. Adrenal masses were subdivided into three classes, AI > 10 mm (according to regening definition of AI; adenoma >10 mm), hyperplasia/ general enlargement and suspected malignancy (metastasises/ adrenocortical cancer).
Results
3467 imaging reports from 2939 individuals performed in 2002 were reviewed. In 2015 > 14000 investigations were performed, of which 5434 CT-scans of 5018 individuals were reviewed (only first 5 months in 2015). The median age in 2002 was 64 years (18–97) and in 2015 66 years (18–101). Adrenal masses were found in 3.0% in 2002 and 4.9% in 2015 ($P<0.05$). 0.6% respectively 0.3% were classified as metastasises. The incidence of AI according to reigning definition (> 10 mm) was 2.0 resp 4.1% ($P<0.05$).
Conclusion
A fourfold increase of performed investigations was observed comparing 2002 to 2015. Consequently, there was an increase of the absolute number of diagnosed AI. In parallel the incidence increased significant from 2.0 to 4.1%, which is relatively low in relation to reports from other cohorts. A direct comparison is though difficult to make due to differences in definition of adrenal masses and the types of CT exams used. The increased incidence is probably an effect of improved image technique in combination with enhanced awareness of AI among radiologists.

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AEP54

Sympathoadrenal system function in patients with multiple sclerosis

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Background
Multiple sclerosis (MS) is a chronic inflammatory autoimmune and neurodegenerative disease of the central nervous system typically affecting young adults. Autonomic dysfunction is commonly detected in patients with multiple sclerosis. Lower response of sympathoadrenal system to various stressors is mainly connected with more developed disease. However, data evaluating sympathoadrenal system function in early MS are limited. Present study investigates stress response in newly diagnosed MS patients, at the time of the first attack of MS.
Methods
We examined 15 MS patients and 15 age, sex, and body mass index matched healthy controls. MS patients were newly diagnosed, untreated, in the time of the first occurrence of the symptoms. Two stressors were used to evaluate the sympathoadrenal response: Stroop word-color interference mental stress test and orthostasis. Plasma levels of epinephrine and norepinephrine, blood pressure (BP), and heart rate were evaluated.
Results
The MS patients have higher heart rate during the first two minutes of orthostasis compared to controls ($P=0.034$). Norepinephrine levels were lower ($P=0.027$) in MS patients in the supine position before the orthostasis, however the following rise was similar to healthy controls. Epinephrine levels were similar in both groups before and during orthostasis. At the end of Stroop test MS patients showed trend to have lower systolic BP ($P=0.055$) and lower epinephrine ($P=0.064$) compared to healthy controls. Norepinephrine response during the Stroop test was unaffected by MS.
Conclusions
We were not able to find clinically significant dysfunction in sympathoadrenal system in newly diagnosed untreated MS patients. The results are supporting the findings that autonomic dysfunction in MS is connected with progression of the disease.
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AEP55

Steroidogenic proteins expression pattern in adrenocortical carcinomas

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Introduction
The majority of adrenocortical carcinomas (ACC) autonomously produce steroids. However, urinary steroid profile of patients with ACC revealed that these tumors secrete and release predominantly intermediate metabolites. This steroid secretion pattern could be attributed to the undifferentiated status of the tumor cells expressing an incomplete pattern of enzymes involved in the steroidogenic cascade.
Aims
Our study aim was to analyze the expression profile of key proteins involved in the steroidogenesis cascade, in different adrenocortical tumors.
Methods
Expression of proteins involved in steroidogenesis, namely steroidogenic acute regulatory protein (StAR), 11β-hydroxylase (CYP11B1), aldosterone synthase (CYP11B2) and 17α-hydroxylase (CYP17A1), were analyzed by immunohistochemistry in ACC ($n=14$), adrenocortical adenomas presenting with Cushing syndrome (ACAc) ($n=11$) and non-functioning adrenocortical adenomas (ACAn) ($n=15$). The percentage of the stained area for each protein was analyzed through a computerized morphometric quantification, the ImageJ software.
Results
CYP11B1, StAR and CYP17A1 expressions were significantly lower in ACC when compared to ACAc. Besides that, ACC presented co-staining cells for CYP11B1 and CYP11B2. CYP11B1 expression has a high discriminative power to distinguish ACC from ACAc with a sensitivity of 100% and specificity of 92%. CYP11B1 and CYP11B2 dual negativity presented a specificity of 100% for the differential diagnosis between ACC and ACAc.
Conclusion
ACC present an incomplete pattern of steroidogenic protein expression, with decreased CYP11B1 and CYP17A1, which could explain the predominant secretion of predominantly intermediate metabolites in ACC patients. In addition, in cortisol secreting tumors, CYP11B1 positivity alone is highly specific for benign lesions.
Funding
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AEP56

Crinecerfont (NBI-74788), a novel CRF1 receptor antagonist, reduces adrenal androgens and precursors in patients with classic congenital adrenal hyperplasia: Results from a phase 2, multiple-dose study

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Introduction
Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21OHD CAH) is a rare genetic disorder resulting in impaired cortisol biosynthesis, increased steroid precursors, and excess androgen production. Inhibition of adrenocorticotropic hormone (ACTH) release via antagonism of the corticotropin-releasing factor-1 (CRF1) receptor could reduce adrenal

androgen production, thereby reducing the amount of exogenous glucocorticoids required for androgen control. This Phase 2 study evaluated the pharmacodynamic effects of a novel, non-steroidal, and selective CRF1 receptor antagonist, crinecerfont (NBI-74788), on adrenal androgens and precursors in adults with 21OHD CAH.
Methods
In a sequential-cohort design, 16 subjects (18–50 yrs) with 21OHD CAH received crinecerfont open-label for 14 consecutive days in one or more of 4 oral dosing regimens: 50 mg QHS (Cohort1); 100 mg QHS (Cohort2); 100 mg QPM (Cohort3); and 100 mg BID (Cohort4). ACTH, 17-hydroxy-progesterone (17OHP), and androstenedione (A4) were measured Q2H during the peak morning period (0600, 0800, 1000 hrs) and averaged at baseline and Day14.
Results
Demographics are provided in the table. Substantial reductions from baseline in peak-morning ACTH, 17OHP, and A4 after 14 days of crinecerfont treatment were observed across Cohorts 1 through 4 (Table). A dose-response in A4 was observed with 100 mg dosing regimens showing superiority over the 50mg dose cohort. Adverse events were mostly mild. There were no clinically significant findings from routine laboratory tests, vital signs, or electrocardiograms.
Conclusions
This study ofcrinecerfont, a novel, selective CRF1 receptor antagonist, demonstrated clinically meaningful reductions of elevated ACTH, 17OHP, and A4 and was well tolerated after 14 days of treatment in adults with 21OHD CAH. Further studies are warranted to evaluate the effects of chronic crinecerfont therapy on adrenal steroid production, clinical endpoints of disordered steroidogenesis, and reduction of supraphysiologic glucocorticoid dosing in adult and pediatric patients with 21OHD CAH.

Table

	Cohort1	Cohort2	Cohort3	Cohort4
Demographics				
Female/Male (n)	4/4	5/2	3/5	2/2
Age (mean±SD, years)	31.1±9.4	32.9±9.7	30.9±10.5	30.8±7.6
Median ACTH (pg/ml) normal range: female 6–58; male 7–69				
Baseline[a]	151	232	470	363
Day14 (%Reduction)[a]	114 (–54%)	53 (–67%)	40 (–69%)	169 (–62%)
Median 17OHP (ng/dl) normal range: female <207; male <139				
Baseline[a]	5352	12821	6451	12214
Day14 (%Reduction)[a]	2090 (–60%)	3710 (–75%)	2695 (–55%)	6092 (–60%)
Median A4 (ng/dl) normal range: ≤39 yrs (female 26–214; male 33–134), >39 yrs (female 13–82; male 23–89)				
Baseline[a]	270	597	299	737
Day14 (%Reduction)[a]	109 (s–21%)	346 (–47%)	90 (–43%)	395 (–52%)

[a]Based on peak morning period (0600, 0800, 1000 hrs) average.

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AEP57

Possible protective influence of KCNJ5 and CACNA1D gene polymorphisms on lipid profile in primary aldosteronism and essential hypertensive patients

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Introduction
Primary hyperaldosteronism (PHA) is the most common hormonal cause of secondary hypertensionconnected with substantially higher cardiovascular morbidity and mortality than essential hypertension (EH). The association between aldosterone excess in PHA and mutations in KCNJ5 and CACNA1D genes has been previously described and the possible relation with gene polymorphisms was to consider. The present study is to assess possible association between polymorphisms of ion channel genes with PHA and cardiovascular risk factors.
Methods
68 hypertensive patients (mean age: 47.57±14, 68 y, 29 men, 39 women) with clinical suspicion of PHA were evaluated for PHA and EH according to the aldosterone concentration before and after the salt loading test. In the whole group cardiovascular risk factors including blood lipid profile and the KCNJ5 rs2604204 A>C and CACNA1D rs312481 C>T polymorphisms were determined. Statistical analysis was performed. Statistical significance was set at P-value<0.05.
Results
PHA was confirmed in 30 patients. In PHA patients and in the the entire studied group the CACNA1D 312481C allele was associated with lower total and LDL cholesterol concentration compared to 312481TT (P=0,0030 and P=0.0067). In the EH group the KCNJ5 2604204C allele was associated with lower LDL cholesterol concentration compared to 2604204AA (P=0.0311). No significant differences in the incidence of studied alleles between PHA and EH groups were observed, however a tendency towards more common occurrence of CACNA1D rs312481T allele in EH than in PHA patients has been noted (P=0.0673).
Conslusion
We postulate (1) possible protective influence on lipid profile of the KCNJ5 2604204C and CACNA1D312481C polymorphism variants. The results suggest that (2) PHA and EH do not differ strong in terms of the incidence of investigated gene polymorphisms, however (3) the occurence of rs312481 T allel of CACNA1D gene appears to be more common in patients with EH. Observations need to be confirmed on larger studies.

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AEP58

Steroid hormones influence systemic sclerosis prevalence

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Introduction
Systemic sclerosis (SSc) is a connective tissue disorder with higher prevalence in females which is characterized by vascular damage, pulmonary hypertension, inflammation and progressive fibrosis of skin and other internal organs such as lung. In the skin it has been shown that dermal adipose tissue atrophy and microangiopathy drive fibrosis development, however which is the underlying mechanism and whether this mechanism is responsible for the female prevalence of the diseases needs to be investigated. Here, we addressed these questions by using fra-2 over-expressing mice as a model of SSc.
Material and Methods
Female and male fra-2 overexpressing mice and wild type littermates were characterized at the age of 16-20 weeks. Ovariectomy was performed at the age of 6-8 weeks and the phenotype was analysed at 20 weeks of age. Lung function was measured using Flexivent system (SCIREQ), immunohistochemical staining for alpha-smooth muscle actin (αSMA) and von Willebrand factor (vWF) was performed to assess vascular remodelling. Inflammatory cell count was performed on bronchioalveolar lavage (BAL) of the mice and the right ventricular systolic pressure was acquired by closed chest hemodynamic measurement.
Results
Characterization of fra-2 over-expressing mice, showed that female transgenic mice have a worse phenotype compared to male, suggesting an influence of sex steroid hormones in the development of the phenotype. Female fra-2 over-expressing mice had worse lung function, higher inflammation and stronger vascular remodelling compared to male, however no differences in right ventricular systolic pressure was detected. Ovariectomy did not influence the phenotype, suggesting that female steroid hormones do not play a role in disease development and progression.

Conclusion
Female fra-2 over-expressing mice develop a more severe phenotype compared to male mice. Which is not influenced by ovariectomy. Further analyses are necessary to elucidate the male steroid hormones contribution to the phenotype of fra-2 over-expressing mice. Additionally, the underlying mechanism, the contribution and regulation of hormonal imbalance in these mice will be elucidated.

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AEP59

Algorithm of staged perioperative hemodynamic management (SPOHM)

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Aim
The introduction of modern pheochromocytoma anesthetic management in a specialized endocrinology center with using of the algorithm of SPOHM.
Materials and methods
The implementation of pheochromocytoma anesthetic management in 65 women during surgical intervention by video assistant laparoscopic adrenalectomy. All patients were used an algorithm of SPOHM: preoperative tableted hypotensive therapy before admission (outpatients); preoperative infusion controlled hypotensive therapy by urapidil and correction of hipovolemia by balanced crystalloid solutions and a colloid solution 4-6 mg/kg were applied on the 2nd stage; intraoperative infusion controlled antihypertensive therapy by urapidil on the 3rd stage under the control of non-invasive hemodynamic monitoring (NIHM) and prevention of adrenal insufficiency with final hypovolemia correction on the last 4th stage.
Results and Discussion
All patients had significantly (P=0,0087) increased levels of daily urine metanephrines up to 3080.8±295.7 mg/24 h (control of 169.3±12.7 mg/24 h). According to SPOHM doxazosin 9.72±0.96 mg twice-daily or urapidil 144.0±11.2 mg twice-daily were used at the first stage. On the second stage performed haemodilution by 6-10% solution of HES or 4% Gelatine and controlled infusion antihypertensive therapy by urapidil in anaverage speed 9.7±1.9 mg/hr. During the third stage infusion rate of Urapidil was 1.25±0.08 mg/min (additionaly, in time of the pheochromocytoma surgical separation, urapidil bolus was administered in dosages 25–50 mg IV when the slightest increasing of blood pressure was detected by NIHM, especially cardiac output changes). On the fourth stage was conducted the prevention of adrenal insufficiency by hydrocortyzon replacementtherapy and hypovolemia. No mortality cases were observed.
Conclusions
The introduction of SPOHM has ensured high efficiency and safety of laparoscopic adrenalectomy under general anesthesia and an absence of lethal cases.

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AEP60

16 year-old woman with abdominal paraganglioma secondary to SDHB mutation

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Introduction
Catecholamine-secreting tumours derived from the adrenal medulla and the nodes of the autonomic nervous system are known as pheochromocytomas or paragangliomas, respectively. Although their clinical manifestations are similar, their differentiation is important from an epidemiological and prognostic point of view and their possibility of being associated with genetic syndromes.
Case Report
We present a case of a 16 year old patient, with no pathological history of interest, who was admitted to our centre after finding elevated levels of 24-hour urine fractionated metanephrine, as well as elevated dopamine, noradrenaline and methoxytyramine. A three-year history of evolution based on repeated cases of holocranial headache, diaphoresis, and skin pallor accompanied, especially in the last months before admission, by typical angina chest pain. In the month prior to admission, she had consulted her family doctor due to the increase in symptoms, and in medical consultation she noted high blood pressure. There was a family history of hypertension in a well-controlled maternal grandmother with 2 antihypertensive drugs.
The metanephrine elevation was confirmed after a second determination made during hospitalization. Likewise, imaging tests (abdominal MRI) were performed for tumour location, which showed the presence of a right para-aortic mass compatible in clinical and biochemical context with an abdominal paranganglioma. An extension study was performed with MIBG-123. The patient was operated by laparotomy after medical treatment with phenoxybenzamine and subsequent beta blocking with atenolol for 20 days prior to surgery. The results of the pathological anatomy were compatible with poorly differentiated paraganglioma with associated lymph node metastases. The levels of ki 67 in the sample was >3%. A genetic study was also requested which was positive for the SHDB enzyme mutation.
After the intervention the patient is asymptomatic. Post-surgical determination of fractionated metanephrines without elevation was requested demonstrating a decrease in levels of fractionated methanephrines and methoxytyramine, with persistence of dopamine elevation.
Conclusion
The study and management of catecholamine-secreting tumours is complex. It is well established that surgery is the treatment of choice but there are controversies about the pre and post-operative management of these patient. With this review we want to clarify the more complex data related to the management of these tumours that not only represent a diagnostic challenge but also a therapeutic challenge.

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AEP61

Pheochromocytoma multisystem crisis presenting with cardiogenic shock and Tako-tsubo cardiomyopathy.

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Introduction
Pheochromocytoma is a rare catecholamine secreting neuroendocrine tumor. We describe a rare case of Tako – Tsubo cardiomyopathy as first manifestation of pheochromocytoma, which later developed into PMC.
Case report
A 39-year-old woman, with no history of arterial hypertension, was admitted to the emergency room with acute headache, severe chest pain radiating to the back, nausea and vomiting. At presentation, patient was in cardiorespiratory distress, tachycardic, tachypneic, with signs of pulmonary edema. Electrocardiogram showed supraventricular tachycardia with minor ST-segment depressions at V_5 through V_6 leads. Transthoracic echocardiography revealed akinesis of the middle segments of the left ventricle (LV), excessive apical and basal LV segments contractions and significantly impaired LV ejection fraction of 35–40%. Blood test analysis showed elevated troponin, significantly elevated brain natriuretic peptide (BNP), metabolic acidosis, together with increased hepatic enzymes. Chest and abdominal CT scan was performed and a massive left adrenal mass of 107×93×137 mm was found, so catecholamine – induced stress related (Tako-Tsubo) cardiomyopathy was highly suspected. Blood samples for plasma metanefrin and normetanefrin were taken to confirm the diagnosis of pheochromocytoma. During first 24-hours sepsis, acute renal failure and hypotension developed, thus intravenous infusion of vasopressors was started. However, patient's hemodynamics became unstable, cardiac function deteriorated – troponin I and BNP increased, hypotension and tachycardia remained despite maximal doses of vasopressors. Intra-aortic balloon pump was implanted and α-blocker labetolol 20 mg per hour intravenously and ß-blocker metoprolol 25 mg orally was started. Hemodynamics was stabilized and oral phenoxybenzamine 10 mg bid was prescribed. On day 9th the intra-aortic balloon pump was removed, the dose of phenoxybenzamine was increased to 40 mg per day. Laboratory analyses showed improvement in renal and liver, echocardiography showed transient previously noted wall motion abnormalities with a normal ejection fraction of >55%. On the 15th day of hospitalization, patient under-

went an exploratory laparoscopy, due to bleeding, turning into a laparotomy and excision of the large left adrenal mass. The pathological analysisand elevated plasma metanefrin and normetanefrin confirmed pheochromocytoma. After operation, patient was stable, her vitals were normal, renal, liver and heart function normalized. During follow-up, serum metanephrines were normal. Also abdomen CT scan showed no tumor recurrence.
Conclusion
Our case showed, that despite the rarity of the tumor, it is important to consider pheochromocytoma in any patient with unexplained cardiogenic shock or left ventricular failure, multi-organ failure, hypertensive crisis or unexplained lactate acidosis, especially, if also febrile.

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AEP62

Reducing short synacthen tests by deriving a novel baseline and 30 min cortisol level for a scottish population

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Introduction
The Short Synachten Test (SST) is the gold standard test for assessing adrenal insufficiency, however these can be time and resource consuming. Improved cortisol assays (Scottish consensus) currently advise a cut-off of 430 nmol/l at 30 minutes . However, there is no clarity about the optimum baseline cortisol level and recommendations range varies from 300 – 500 nmol/l. The aim of this study was to establish a single baseline cortisol concentration cut-off which could reliably exclude adrenal insufficiency for this Scottish sub-population. We also assessed if both 30 minute and 60 minute SSTs have clinical necessity.
Method
188 SSTs performed over a 1 year period (2016–2017), at the Victoria Hospital in Fife, were retrospectively analysed for indications, results (baseline, 30 and 60 minutes) and if on long term (LT) steroids. Receiver-operating characteristic (ROC) curve analysis was then performed to assess the optimalserum cortisol level and cut-off for the SSTs.
Results
Out of the 188 patients, 77% ($n=145$) passed the SST at 30 minutes, 6% (11) passed only at 60 minutes and 17% (32) failed at both time cut-offs. A total of 47% (87) patients were on LT steroids. These accounted for 70% (22) that failed overall but represented 80% of those that required the 60 minute test to pass. ROC curve analysis identified a cut-off level of 350 nmol/l (94% specificity and 28% sensitivity) for 30 minute cortisol. This excluded 2 patients who failed the SST. A further cut-off level of 250 nmol/l increased specificity and sensitivity to 91% and 57% respectively, but excluded 3 patients that failed.
Discussion
This study showsthat only a 30 minute SST is required in most cases to identify adrenal insufficiency. This reduces the time and financial costs associated with SSTs. However, 60 minute SSTs should be considered in patients on LT steroids, acutely unwell or with a pituitary disorder. This study suggests that a novel cortisol cut-off level of 350 nmol/l at 30 minutes in a SST can be safely used to identifypatients with adrenal insufficiency in a Scottish population. It also suggests a novel morning baseline cortisol level of <250 nmol/l can be used to classify SST requirement. Limitations to this study include the small population sample, the large number on steroids and unknown timings of the SSTs. Further studies in a larger population size shall be performed to confirm these results.

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AEP63

Surgical outcomes of adrenalectomy for primary hyperaldosteronism after using novel diagnostic tests

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Background
Primary hyperaldosteronism (PHA) is the most frequent type of endocrine hypertension with a prevalence that is continuously rising. Following the introduction of diagnostic tests that consider both the adrenocorticotropic hormone effect andrenin–angiotensin–aldosterone system (RAAS), the post-dexamethasone saline infusion test (D-SIT) and the overnight dexamethasone, captopril, valsartan test (DCVT) using pharmaceutical RAAS blockade, a higher prevalence of PHA was found.
The aim of the study
To validate in the utility of the newly introduced diagnostic tests in pre- and post-surgical setting. The normal cutoffs values post-D-SIT were for aldosterone 67.59 pmol and for aldosterone-to-renin-ratio (ARR) 9.74 pm/mU/l, whilst post-DCVT for aldosterone 85 pmol/l and for ARR 9 pmol/IU.
Results
We studied 41 patients (16 males), with median (IQR, range) age 50 (16, 35–74) years. The median size of the adenoma resected was 2.1 (2.5, 1–6.5) cm, and in 21 patients was left-sided. Twenty-nine out of 31 were cured by the D-SIT, with aldosterone suppression; 4 patients had ARR >9.74 pm/mU/l but with suppressed aldosterone levels. In 6 patients PHA was diagnosed by DCVT criteria and one by both DSIT and DCVT; 2 patients were found cured post-adrenalectomy by DCVT criteria whereas the rest of the patients displayed low blood pressure measurements post-surgery. Overall, only 2 patients failed to be cured post-surgery implying an adrenalectomy success rate of 95.1%. In 40 patients post-adrenalectomy, 12 (30%) did not change their therapeutic anti-hypertensive status (remained without treatment if not previously treated or retained the same drugs and doses), 23 (57.5%) showed improvement (discontinued their anti-hypertensive treatment or reduced number and doses of anti-hypertensive drugs) and 5 (12.5%) had deterioration (anti-hypertensive treatment or drugs dose increase). A subset of 15 patients out of 32 diagnosed by D-SIT criteria did not suppressed cortisol levels post-dexamethasone suggesting a high percentage of mixed adenoma. The majority 9 patients had cortisol levels between 51 and 138 nmol/l whilst 6 patients had>150 implying autonomous cortisol secretion. Post-surgery, all 33 patients submitted on D-SIT suppressed cortisol levels.
Conclusion
The present study is a proof of concept for the validity of the newly introduced diagnostic tests for PHA in the clinical practice. The novel tests show a similar rate of clinical and biochemical response post-adrenalectomy, but may better discriminate the cases that may recur.

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AEP64

Subtyping of primary aldosteronism in patients with partially successful adrenal vein sampling

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Introduction
Adrenal vein sampling (AVS) is a gold standard in the assessment of the cause of primary aldosteronism (PA). It is technically demanding procedure having the high rate of failure, even in expert centres. Our study aimed to investigatewhether the data on aldosterone and cortisol concentration from successfully cannulated adrenal vein could determine the subtype of PA in certain patients with partially successful AVS.
Materials and methods
The study included 36 AVS procedures performed in 35 patients (one patient undergone AVS twice). Unilateral aldosterone secretion was confirmed in 12 patients who were all surgically treated and achieved biochemical remission of the disease. In the remaining 23 patients, AVS results were consistent with bilateral adrenal hyperplasia. In all patients aldosterone/cortisol ratio between the peripheral and adrenal veins, as well as aldosterone/cortisol ratio in adrenal veins were analysed.
Results
Statistical analysis, using ROC curve, showed that peripheral/adrenal vein aldosterone/cortisol ratio>2.3 (100 % sensitivity, 88% specificity) OR aldosterone/cortisol ratio in adrenal vein<0.64 (92% sensitivity, 93% specificity) indicate unaffected adrenal gland.

Conclusions
Aldosterone/cortisol ratio in adrenal vein of <0.64 and aldosterone/cortisol ratio between the peripheral and adrenal vein of >2.3 are consistent with unaffected adrenal gland indicating that excess aldosterone secretion originates from the opposite side.

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AEP65

Patients with adrenal insufficiency have cardiovascular features associated with hypovolemia

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Context
Patients with adrenal insufficiency (AI) have excess mortality and morbidity, mainly due to cardiovascular diseases. The mechanisms for this is unclear.
Objective
To assess cardiovascular structure and function in AI patients on conventional replacement therapy and after switching to once-daily, modified-release hydrocortisone (OD-HC).
Methods
The analysis included 17 adult AI patients (11 with primary AI, 7 with secondary AI)on stable replacement with cortisone acetate [median (minimum, maximum) 33.5 (12.5–50) mg] and, if needed, fludrocortisone [0.1 (0.05–0.2) mg], and 17 healthy matched controls. Ten patients switched to an equivalent dose of OD-HC. Echocardiography, 24-hour Holter-ECG and 24-hour blood pressure monitoring were performed at baseline and 6 months after the switch to OD-HC.
Results
At baseline, AI patients had smaller left ventricular diastolic diameter (47.1±4.2 vs 51.6±2.3 mm; $P=0.001$) and left atrial diameter (34.9±4.7 vs 38.2±2.6 cm; $P=0.018$), and a higher ejection fraction (62.5±6.9% vs 56.0±4.7%; $P=0.003$) than controls. AI patients had lower nocturnal systolic and diastolic blood pressure than controls (108.3±14.7 mmHg vs 117.2±8.3 mmHg; $P=0.038$ and 65.1±9.4 vs 72.9±6.6 mmHg; $P=0.008$, respectively). After the switch to OD-HC, nocturnal diastolic blood pressure normalised. No significant changes were observed in echocardiographic and Holter-ECG parameters following the switch.
Conclusions
AI patients on conventional treatment display cardiovascular abnormalities that could be related to hypovolemia. Switch to OD-HC seems to have beneficial effect on blood pressure profile, but no effect on cardiovascular structure and function.

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AEP66

Indications for aldosterone/renin screening presented by patients later diagnosed with hyperaldosteronism in a general endocrinology outpatient clinic

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Introduction
Endocrine Society guideline indications for screening (EGS) of hypertensive patients for hyperaldosteronism are not universally followed in clinical Endocrinology. We present a series of patients with hyperaldosteronism, diagnosed following strict EGS compliance.
Methods
Retrospective. Following compliance with EGS in all patients attended in a general Endocrinology outpatient clinic, 70 hypertensive patients were diagnosed with hyperaldosteronism over an 8-year period. Screening, with determination of the Aldosterone (RIA)/direct renin (RIA) ratio (ARR), was considered positive when ≥20 in patients on hypertension medication, excluding spironolactone, eplerenone, amiloride. The 2-hour 25 mg captopril test was performed following a minimum of 2 weeks solely on doxazosin, slow-acting verapamil, and/or hydralazine, at least 6 weeks off spironolactone, eplerenone, amiloride. Hyperaldosteronism was diagnosed when the 2-hour aldosterone level (in pg/ml) was ≥130, and/or the 2-hour ARR was ≥50. Interquartile Range in brackets.
Results
40/70 (57.1%) women, mean age: 63.01 (SD:11.9). Hypertension diagnosed 12.6 (SD: 10.8) years earlier.
Reasons for Referral
Thyroid disease: 19/70 (27%), Diabetes 14/70 (20%), normokalemic hypertension 10/70 (14.3%), obesity 5/70 (7.1%), first-degree relatives (FDR) of hyperaldosteronism patients 5/70 (7.1%), adrenal incidentaloma 4/70 (4.7%), hyperparathyroidism 4/70 (5.7%), hypokalemic hypertension 2/70 (2.8%), others 7/70 (10%).
Indications for screening
Severe hypertension 35 (50%), moderate hypertension 31 (44.3%), resistant hypertension 17 (24.3 %), spontaneous hypokalemia 6 (8.6%), diuretic-induced hypokalemia 13 (18.6 %), hypertension <40 years of age 10 (14.3 %), FDR 6 (8.6%), Incidentaloma 5 (7.1 %). 35/70 (50%) presented 1 indication for screening, 22 (31.4 %) had 2, and 13 (18.5%) had ≥3. The latter presented a higher 2-hour median serum aldosterone: 214 [169.3-350.8] versus those with 2:174 [139.5-245.5] or 1 indication: 147 [120-181.5] $P=0.008$. Moderate hypertension was the sole indication in 16/70 (22.9%). The median screening ARR was higher in patients with resistant hypertension: 109 [41.5-232] than in the rest: 55 [35.15-92.13], $P=0.047$. Median aldosterone screening levels were higher in patients with severe hypertension: 248[152-338] than in the rest:190[132-245], $P=0.028$, as was 2-hour serum aldosterone: 201 [141-279.5] versus 151 [121-186.5], $P=0.016$.
Conclusions
Almost half the patients diagnosed with hyperaldosteronism in Endocrine Clinic had been referred for treatment of thyroid disease or Diabetes. Only 8.6% of patients presented spontaneous hypokalemia. Given the elevated morbimortality associated with hyperaldosteronism, Endocrinologists should study ALL their hypertensive patients presenting indications for screening, regardless of the reason for referral. Screening should not be limited to patients with adrenal incidentaloma or hypokalemia.

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AEP67

Hyperparathyroidism in patients with overt and mild primary aldosteronism: Epidemiological data from a tertiary centre

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Introduction
Primary aldosteronism (PA) is the most common cause of endocrine hypertension. In recent studies, increased prevalence of hyperparathyroidism (HP) has been observed in PA patients. However, the prevalence of HP in overt or milder forms of PA has not been evaluated yet.
Objectives
To estimate the prevalence of HP in patients with PA (overt and milder forms) and investigate the effect of treatment (eplerenone or surgery) on PTH secretion.
Patients and methods
We included prospectively 60 (39 men) PA patients (mean age 58.4±11 years) with normal renal function. The diagnosis of PA was based on the combination of valsartan, captopril and dexamethasone suppression test (DCVT)[1]. The patients were divided in two groups: overt (based on basal aldosterone/renin ratio (ARR)>84 pmol/mU[2] and positive DCVT) and mild PA (based only on positive DCVT). Mean systolic (SBP) and diastolic (DBP) blood pressure, iPTH, 25OHD, serum and 24 h-urinary calcium, potassium and phosphate levels at time of PA diagnosis and after surgical or medical treatment with eplerenone were evaluated.

Results
Primary HP was found in 5% (3/60) and secondary HP in 51.6% (31/60). Overt and mild PA was found in 40% (24/60) and 60% (36/60) respectively. Fifty one out of 60 PA patients were followed-up for 11 ± 6months, without receiving supplementary vitamin D treatment. After treatment, there was a significant decrease of mean SBP and DBP ($P<0.001$), iPTH ($P<0.001$) and 24 h-urinary calcium ($P<0.001$) and a significant increase of serum potassium ($P<0.001$), corrected Calcium ($P=0.01$) and 25OHD ($P<0.001$) levels in both primary and secondary HP patients. Furthermore, there was no significant difference between patients with overt and mild PA, concerning the iPTH, serum calcium and 25OHD levels, neither prior or after treatment. Aldosterone levels before treatment were positively correlated with serum PTH levels ($P=0.04$).
Conclusions
The prevalence of HP was found to be particularly high in PA patients, both in overt and mild cases. Treatment has a significant impact equal in overt and mild PA on serum calcium, 25OHD and iPTH levels, suggesting an association between mild or overt PA and primary or secondary PH.
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AEP68

Does adrenal vein sampling really improve the final approach for treating prymary aldosteronism? a retrospective study.
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Introduction
Primary aldosteronism (PA) causes 15–25% of cases of drug-resistant hypertension (RBP). Adrenal vein sampling (AVS) is considered the gold standard for diagnosis of aldosterone aberrant secretion origin. The distinction between unilateral and bilateral disease dictates the targeted therapeutic approach, with surgery for aldosterone producing adenomas and medical therapy for patients with bilateral hyperplasia. As AVS is an invasive, not well standardized procedure and it is restricted to few specialized centers, several attempts have been made to simplify diagnostic algorithms by using abdominal imaging only. We aimed to compare how AVS changed the approach firstly chosen by CT-scan at our hospital.
Methods
A retrospective study in a single referral center was performed. All cases diagnosed with PA and in which CT scan and AVS were carried out, between 2006 and 2019, were included. We compare the CT scan-AVS concordance and we analyze the clinical decision that was taken and its result in terms of blood pressure control. For asses sampling quality we used an index cutoff of 1.1.
Results
We included 36 patients. 21 men/15 women. Mean age 60.8 y.o.. Diagnosis of PA was made due to suspicion of secondary RBP in 34 patients and due to an adrenal incidentaloma in 2 patients. CT-scan showed unilateral adenoma in 28 patients and hyperplasia or bilateral adenomas in 8 patients. In AVS, left AV was adequately sampled in 97% and right AV in 78%. In 20 patients (55,5%) AVS and CT-scan agreed, thus, initial therapeutic achievement did not change. In 12 patients, CT-Scan showed unilateral adenoma but AVS displayed no lateralization. All these patients were treated successfully with medical therapy except 2 patients who underwent surgery. One was cured but in other HBP persisted. In 3 patients, CT-scan showed bilateral disease but AVS displayed lateralization. One was treated with surgery and was cured. Other was treated successfully with drugs and other is waiting for surgery. Finally, one patient presented with a right adenoma and AVS displayed left lateralization. She was treated medically. Overall, 18 (50%) patients have been operated, and RBP has been cured in 8 and the rest has significantly reduced the number of antihypertensive drugs.
Conclusion
In 55% of patients, AVS confirms the abdominal imaging and the initial approach would not change. However, in 43% of patients AVS and CT-scan did not correlate. Thus, AVS can significantly improve the choice of treatment modality.
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AEP69

Pulsatile subcutaneous hydrocortisone replacement in primary adrenal failure, a proof of concept pilot trial
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Background
The pulsatile endogenous cortisol secretion is crucial for ultradian rhythmicity in blood and this rhythmicity triggers pulses of gene signaling in tissues. Disturbances in cortisol pulsatility can lead to cognitive, metabolic and cardiovascular dysfunction, and could explain why patients with primary adrenal insufficiency on conventional glucocorticoid replacement have reduced quality of life, increased mortality and are at risk of cardiovascular complications. Pulsed subcutaneous cortisol administration could be a means reversing and preventing these complications.
Objective
Comparison of three treatment regimen: conventional tablet treatment, continuous subcutaneous hydrocortisone infusion (CSHI), and pulsatile subcutaneous hydrocortisone infusion (USHI).
Study design
An open labelled, two weeks crossover, clinical trial
Participants
Two participants with Addison's disease, one adrenalectomized and two with congenital adrenal hyperplasia . All participants signed informed consent before entering the study.
Intervention
All underwent treatment with standard oral hydrocortisone, USHI and CSHI for two weeks in each treatment arms. USHI delivered hydrocortisone in seven bolus doses every three hours. Microdialysate from adipose tissues was obtained continuously and collected in fractions, each covering 20 minutes. Blood samples were taken every 20 minutes in the morning, hourly in the afternoon hourly and every other hour at night. Samples were assayed for glucocorticoids by liquid chromatography mass spectrometry.
Results
We restored the pulsatile oscillation of cortisol in serum and in subcutaneous tissue in the morning hours, the maximum levels of cortisol were between 350–495 nmol/l. The midnight maximum levels of cortisol were between 90–45 nmol/l. ACTH levels were in normal range during day time during both USHI and CSHI treatments compared with large oscillation on oral treatment. ACTH-levels started to raise about 0100 h and were significantly lower on USHI treatment from 0330 h compared to CSHI and oral treatment. Levels of androgens oscillated in the same pulsatile fashion as cortisol.
Conclusion
We show that mimicking the physiological ultradian cortisol rhythm is possible with pulsatile hydrocortisone treatment, resulting in reduction of ACTH levels.
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AEP70

CAH-X Syndrome in a german cohort of patients with 21-hydroxylase deficiency
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Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (CAH) is encoded by the CYP21A2 gene. The CYP21A2 gene is partially overlapped by the TNXB gene encoding an extracellular matrix protein called Tenascin-X. Deficiency of Tenascin X can cause the Ehlers-Danlos Syndrome (EDS). Deletions of CYP21A2 extending into TNXB rarely cause CAH combined with EDS. CAH associated with mild hypermobility form of EDS due to TNXB haploinsufficiency caused by heterozygous mutation has been named CAH-X syndrome. We genetically investigated a cohort of 81 patients (31 males, mean age 37.8 years ±9.8) with classic CAH for CAH-X. Patients genetically positive for CAH-X and unaffected CAH

control patients matched for sex, age and BMI underwent a thorough clinical investigation including joint examination by Beighton 9-point scale, skin and neurological examination, by a standardised protocol of thransthoracic echocardiography and muscle ultrasound. In addition serum tenascin-X has been measured. We identified one patient with CAH and EDS and 4 patients with CAH-X. All CAH-X patients had concentrations of tenascin-X below the normal range, but not different from 35 unaffected CAH patients. All 4 patients with CAH-X showed some associated clinical symptoms. Two had joint hypermobility detected by Beighton 9-point score. Two CAH-X patients showed cardiac abnormalities. The patient with CAH and EDS showed cardiac abnormalities and typical EDS symptoms. All affected patients complained about back pain and showed foot malposition. Profound changes in muscle ultrasound were found in 60 % of patients with CAH-X syndrome (3/5) and in none of the controls (0/5). In conclusion, our data confirm the previously described prevalence of CAH-X. Beighton-score seems to be a quick and cheap screening instrument for CAH-X and should be performed in all patients with classic CAH, since protein level in serum cannot be used for screening for CAH-X-Syndrome. A stronger focus needs to be made on back pain and foot malposition as symptoms of CAH-X and echocardiography should be performed in all CAH-X patients. Therapy should depend on clinical symptoms.

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AEP71

Cardiovascular risk and metabolic profile in adult patients with congenital adrenal hyperplasia

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Background
Classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is characterized by impaired cortisol synthesis, requiring life-long glucocorticoid (GC) replacement therapy. Given the detrimental systemic effects of GCs in the long term, the aim of our study was to assess whether CAH patients have increased metabolic and cardiovascular alterations compared with age-matched controls.
Materials and methods
For this cross-sectional study 29 patients with CAH were submitted to biochemical and hormonal testing, oral glucose tolerance test (OGTT), intima-media thickness (IMT) evaluation and compared to 21 controls matched for age, sex, BMI and smoking-habits. The effects of different GC regimens (dexamethasone, DEX vs dual-release hydrocortisone, DR-HC) on metabolic parameters and quality of life were also assessed.
Results
IMT was higher in CAH than in controls at right and left common carotids (0.8±0.3 vs 0.68±0.12 mm, $P<0.001$ and 0.8±0.35 vs 0.68±0.17 mm, $P<0.001$) and carotid bulbs (0.8±0.2 vs 0.64±0.18 mm, $P<0.0001$ and 1±0.35 vs 0.62±0.13 mm, $P<0.0001$). Patients on DEX treatment had taken lower cumulative GC dose during the last 3 years compared to those on DR-HC and daily dose normalized for body surface area (7.18±4.18 and 10.77±2.76 mg/m^2, $P=0.045$). Despite lower equivalent doses, patients taking DEX showed better disease control with lower 17-hydroxyprogesterone (respectively, 40.5±230.76 vs 741±893.5 nmol/l, $P=0.008$) and ACTH (respectively, 32±58 vs 652.5±855.25 ng/l, $P=0.016$). However, DEX therapy was associated with higher glucose levels during OGTT with an overall more elevated $AUC_{-glucose}$ (32.9±9.58 vs 21.45±6.77, $P=0.005$) than DR-HC without differences in insulin curves. To add, DEX induced an increase in clotting factors II (143.95±35.55% vs 109.55±25.5%, $P=0.039$) and X (106±6.24% vs 96.5±8.2%, $P=0.05$), followed by a compensatory increase in antithrombin (106±6.24% vs 96.5±8.2%, $P<0.005$), protein C (113.8±23.99% vs 92.35±27%, $P=0.006$) and plasminogen (108.9±17.04% vs 89.5±28.03%, $P=0.025$) compared to DR-HC.
Conclusions
Patients with CAH have a higher cardiovascular risk which is probably due to both chronic GC treatment and the disease itself. The negative effects of GCs on glucose metabolism and coagulative cascade depend not only on the total GC dose, but also on the type of drug taken and probably on its time of administration. DEX proved to be effective in suppressing adrenal androgen secretion to the detriment of a less favourable glucose profile. Conversely, DR-HC, even administered at higher equivalent dose, did not guarantee a comparable disease control, but showed a lower metabolic impact. Our results pinpointed the need to individualize GC therapy in CAH on the basis of each patient's characteristics.

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AEP72

Adrenal incidentalomas and renal cysts – the definitive sign of aging?

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Introduction
The prevalence of adrenal incidentalomas (AI) and renal cysts increase with age. Depending on the study population age and sex, on average, both are prevalent with about 8 to 10% in subjects older than 50 years of age.
Aim
We aimed to investigate the co-occurrence of AI and simple renal cysts.
Methods
Our study included 970 subjects, 494 with AI – all evaluated in single centre, and 476 control group (CG) patients (not harboring AI) enrolled from trauma patients admitted to the emergency room with performed CT scan of abdomen. Patients with polycystic kidney disease, end-stage kidney disease, hydronephrosis and known malignant diseases were not included in the study.
Results
There was no significant difference in age (AI: 60.79±10.26 years, CG: 61.80±9.59 years, $P>0.05$) nor gender (male/female, AI: 163/330, CG: 181/295, $P=0.107$) between AI and CG. Simple renal cysts were significantly more prevalent in patients with AI than in CG, 33.1% vs 19.5%, $P<0.001$. In both groups patients with cysts were significantly older than those without them (AI: 62.45±9.00 vs 56.99±10.38 years, $P<0.001$ and CG: 64.20±9.26 vs 61.22±9.59 years, $P=0.007$, respectively). Gender distribution was the same between patients with and without cysts in both study groups. Among AI patients the presence of cysts was not dependent on the level of cortisol suppression in 1mg dexamethasone suppression test (cortisol: <50 nmol/l, $P=0.661$ and <140 nmol/l, $P=0.248$). The prevalence of renal cysts among unilateral and bilateral tumours was the same ($P=0.814$) and it was not dependent on the size of the adrenal tumour.
Conclusion
Patients with AI are more likely to harbor a renal cyst(s) then patients without AI. Also, our study points to the significance of aging to occurrence of both AI and renal cysts.

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Major barriers exist in the diagnosis and management of addison's disease in africa

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Background
The burden and management of Addison's disease (AD) in Africa have not been well documented. We aimed to identify specific disease characteristics, patient demographics and patterns of clinical management in established AD in Africa, hypothesizing that deficiencies in diagnosis and management exist.

Methods
An on-line survey of a large pool of medical practitioners' experience from Africa and Middle East, relating to AD was conducted, using a commercial database.
Results
Respondents: Of the 1334 responses received, 589 provided complete data and of these, 332 respondents confirmed that they manage patients with hypoadrenalism. Patients: Data obtained referred to 5787 patients with hypoadrenalism (2746 females, 3041 males), of whom 2302 had primary hypoadrenalism (AD). The likely causes of AD in sub- Saharan Africa (SSA) vs Middle East North Africa (MENA) included autoimmune disease (20% vs 60.3%; $P<0.001$), tuberculosis (34% vs 4.1%; $P<0.001$), AIDS (29.8 % vs 1%; $P<0.001$). Most patients 83.7% presented with typical AD symptoms, however 376 patients (16 %) presented in an Addisonian crisis in both regions. Non-availability of diagnostic tests across both regions included tetracosactide in at least 45.7%, serum cortisol 50.7% adrenal antibodies (64.1%), and adrenal CT scans (49.1%). They were managed using hydrocortisone alone in SSA 588 (39.9%), compared with MENA 780 (94.2%); $P<0.001$, whereas fludrocortisone was only available in 36% of the entire cohort. Some form of medical emergency identification was used in only 241 patients in SSA (16.4%) vs 493 (59.6%) MENA patients; $P<0.001$.
Conclusions
Significant hurdles in diagnosing AD in Africa include poor availability of tetracosactide by plasma cortisol as a surrogate, adrenal autoantibodies and CT scans of the adrenal glands, all proven diagnostic utility. Fludrocortisone is also poorly available. It is expected that these findings may account for inadequate diagnosis, management of AD with potential fatal consequences.

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AEP74

Acute adrenal failure as presenting feature of antiphospholipid syndrome

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Introduction
Anti-phospholipid syndrome is characterised by the presence of arterial or venous thrombosis, it is autoimmune in nature and manifests as a systemic disease. Adrenal vein haemorrhagic infarction which is a sequel of adrenal vein thrombosis ultimately leads to loss of adrenal function, it is one of the presentations of anti-phospholipid syndrome especially with catastrophic type. In one analysis adrenal involvement was reported in only 13% of the reported cases of a catastrophic type of anti-phospholipid syndrome.
Case report
A 64-year-old man presented with generalised fatigue, dizzy spells nausea, vomiting, and vague abdominal pain. His past medical history includes previous admission with pneumonia complicated with right leg deep venous thrombosis. At that time a thrombophilia screen was performedand revealed positive anticardiolipin (serum level of >120 U/ml) and anti-B-2 glycoprotein antibodies (268 RU/ml). Hence the patient was diagnosed with antiphospholipid syndrome secondary to pneumonia. At the time of admission, he looked plethoric, his blood pressure was 90/45 mmHg, and no significant systolic drop in blood pressure was noted. The blood sugar level was 4.0 mmol/l. Initial investigations revealed serum sodium 129 mmol/l (136–145 mmol/l) potassium t 5.7 mmol/l (3.6–5.1). APTT of 72 seconds (28–40). ESR 73 mm/hr (1–14). Given the clinical presentation, the low sodium, and the high potassium, synacthen test was performed. Pre synacthen serum cortisol was 41 nmol/l (119–618 nmol/l) and post synacthen cortisolwas 43 nmol/l (> 450 nmol/l), indicating no significant response to ACTH. Adrenal antibodies were negative. Abdominal ultrasound revealed a left kidney cyst measuring 3 cm in maximum diameter. This led to a CT scan of the abdomen that showed enlarged adrenal glands bilaterally. Urinary catecholamines and VMA were requested and werewithin the normal range. A PET CT was done to rule out malignant enlarged adrenal gland and showed no FDG avid macroscopic disease. Serum QuantiFERON sample was requested as TB remains an important cause and revealed strongly positive result. Anti-tuberculosis treatment was started in view of evidence at hand. Regular follow up plan put in place. Five months after the initial scan, a repeat scan showed a significantly reduced size of adrenal glands to 1.3 cm .After reviewing the serial scans at MDT discussion the initial diagnosis was revised and the MDT Consensus washaemorrhagic infarcts secondary to anti-phospholipid syndromeas the final diagnosis.
Conclusion: APS should be considered as a cause of hypoadrenalism even though it is a very rare cause.

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AEP75

Differential diagnosis of primary adrenal insufficiency in a young male with mental retardation and axonal sensorimotor polyneuropathy

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Introduction
Primary adrenal insufficiency (PAI) is a rare disease with a prevalence of 82–144 cases/milion. The etiology of PAI is represented primarily by autoimmune adrenalitis, followed by tuberculosis and less common by fungal infections, HIV, hemorrage in adrenal glands, certain drugs and by some genetic disorders such as Triple A syndrome (AAA), Adrenoleukodystrophy (ALD), congenital adrenal hypoplasia, congenital adrenal hyperplasia, etc.
Case presentation
A 19-years old male diagnosed with moderate mental retardation is admitted to our clinic complaining about the appearence of few dark spots on his tongue and chronic dysphagia for both solids and liquids. He has a sister with subclinical hypothyroidism and his mother, with type 2 diabetes mellitus, suffered a myocardial infarction at 40 years old. Clinical findings included: BMI = 17.9 kg/m^2, generalized hyperpigmentation of teguments and darken patches on the dorsal surface of his tongue, normal body and facial hair, important muscular hypotrophy on lower limbs, bilateral pes cavus and hammer toes. Blood pressure was 100/60 mmHg with no postural variation. Adrenal insufficiency was confirmed by low 0800 h serum cortisol (1.92 µg/dl; normal values: 6-22 µg/dl) with high ACTH (1320 pg/ml; normal values: 16-65 pg/ml), low-normal aldosterone level in upright position (25.3 pg/ml) and normal renin. Thyroid function, antithyroglobulin and anti-TPO antibodies, 17-OH progesterone, testosterone, LH, FSH, PTH and electrolytes were in the normal range. Abdominal computed tomography revealed enlarged left adrenal gland. The patient started replacement therapy with 20 mg hydrocortisone and 0.1 mg fludrocortisone per day. We excluded tuberculosis. Neurological examination revealed peripheral axonal sensorimotor polyneuropathy. The MRI of the brain showed a 9.5 mm arachnoid cyst, no signs of demyelination and no imagistic arguments for leukodystrophy. Further investigations, 21-hydroxylase antibody, very long chain fatty acids (VLCFA) levels and esophageal manometry, are needed in order to establish the etiology of PAI.
Conclusion
Even though the primary etiology of PAI is autoimmune, in some patients additional testing should be performed in order to exclude genetic causes. Early diagnosis of these conditions may reduce morbidity and improve quality of life in these patients.

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AEP76

Bronchogenic cyst mimicking adrenal mass

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Introduction
Primary retroperitoneal bronchogenic cysts are rarely seen. Bronchogenic cysts are mostly benign which originate from the remnants of the primitive foregut during the embryonic development.
These lesions can be seen near or inside any organ that originates from the embryonic foregut. Bronchogenic cysts are most often found in the thoracic cavity, especially in the mediastinum. Except this many distant sites, such as abdomen, retroperitoneum, left ventricle have been reported. A bronchogenic cyst, which was defined in the retroperitoneal region, was first described

by Miller et al. in 1953. No specific diagnostic imaging modality is present for the preoperative diagnosis of retroperitoneal bronchogenic cysts. This is why a bronchogenic cyst may be misdiagnosed as an adrenal tumor or other retroperitoneal lesions. Definite diagnosis requires histopathological examination. Here, we report a case of a 28-year-old male with a bronchogenic cyst mimicking as an adrenal mass.
Case
A 28-year-old male was admitted to the hospital after having intermittent left flank pain. There was no significant findings in his physical examination, and in the laboratory analysis kidney and liver function test values were within normal limits. Abdomen computed tomography was performed and in the left surrenal gland a 42 × 36 mm large lesion with 38 HU density without contrast enhancement was observed. The patient was tested for hypercortisolism and pheochromocytoma. Primary hyperaldosteronism was not examined because he had no history of hypertension. After the test results the adrenal mass was considered as nonfunctional. Because of the size of the mass, the patient was operated and left adrenelectomy was performed. Macroscopically, the specimen consisted of a regular, cystic mass measuring 50 × 40 × 35 mm. It was observed that the mass was attached to the adrenal gland but not infiltrated into the adrenal parenchyma. After histopathological analysis the concise diagnosis was made as bronchogenic cyst.
Conclusion
We present an uncommon bronchogenic cyst mimicking adrenal mass in a 28-year-old male who admitted with left flank pain. Bronchogenic cysts are rare and often benign lesions. Like most adrenal lesions, bronchogenic cysts are frequently asymptomatic and diagnosed incidentally. Bronchogenic cysts should be considered in the diagnosis of lesions located in the retroperitoneal region.

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AEP77

Primary aldosteronism : Study of 09 cases

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Introduction
Primary aldosteronism (PHA), also known as primary hyperaldosteronism or Conn's syndrome, refers to the excess production of the hormone aldosterone from the adrenal glands.
Study objectives
To show clinical, biochemical, and morphological data of 09 patients with primary hyperaldosteronism as well as the therapeutic choice for each patient
Mehtods
it is aretrospective and descriptive study of 09 cases with primary hyperaldosteronism, which were admitted between 2014 and 2019.
Results
Our series included 5 women and 4 men. The mean age of our patients was 44 years. All had severe blood pressure at the time of diagnosis with a median of 190/101 mm Hg varying between 240 and 150 mm Hg for systole and between 120 and 80 for diastole. The mean age of onset of hypertension was 32 years. The context of screening of PHA was severe and resistant hypertension in 89% of the cases followed by the association of hypertension and hypokalemia in 67% of the cases. Sixty-seven percent of our patients had hypokalemia at the time of diagnosis, while 33% had normal serum potassium.
PAH was mentioned and then confirmed by a high aldosterone / renin ratio in 89% of patients with values varying between 63 and 195 (122.42 on average) when standing and then lying down with values varying between 25 and 840 (178 on average). CT scan showed bilateral adrenal hyperplasia in 4 cases, Conn's adenoma in 3 cases, and unilateral hyperplasia in one case. Four patients had an adrenalectomy under laparoscopy while 5 patients were put on medical treatment. Seventy-five percent of our operated patients had complete remission with normalization of blood pressure while only 40% for patients on medical treatment. The serum potassium level normalized for all patients.
Conclusion
At the end of this work, concerning the management of the 9 cases of PAH treated at the Avicenna Military Hospital in Marrakech, it seems important to insist on the methods of management of this pathology, which must be multidisciplinary including endocrinologists, cardiologists, radiologists, urologists and biologists.

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Adrenal necrosis caused by streptococcus constellatus infection

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A 49-year-old man who has diabetes mellitus and alcoholic cirrhosis presented to the emergency department due to left upper quadrant abdominal pain and left back soreness for three days. He received sclerotherapy and endoscopic band ligation twice for gastric varices few months prior to admission. On physical examination, he had rebound tenderness at left upper abdomen. The computed tomography (CT) of abdomen revealed diffusely enlarged left adrenal gland with rim-enhanced multi-cystic components and necrosis in pararenal space. One of the two peripheral blood culture yielded streptococcus constellatus. The adrenal hormones were all within normal limits. CT-guided biopsy of the left adrenal gland was performed. The pathology revealed only necrosis with reactive change, and the results of special stains and culture were both negative. The symptoms were resolved after intravenous broad-spectrum antibiotic agents and he continued 6-month course of oral cefixime at outpatient department. During the antibiotic treatment, the Gallium scan showed grossly normal and no definite gallium accumulation at the suprarenal/perirenal soft tissue. The follow-up CT scan showed partial resolution of infiltrative left adrenal lesion after 2-month treatment, and smaller size of left adrenal lesion after 5-month treatment. However, fever with chills and abdominal fullness developed three months after discontinuation of the antibiotic treatment. The CT scan showed enlargement of left adrenal lesion, and recurrent infection or inflammation was suspected. Antibiotic treatment was given again. The peripheral blood culture revealed negative finding. He received CT-guided drainage, and 5 ml yellowish pus was drained. The culture from CT-guided aspiration this time yielded streptococcus constellatus. The patient then received laparoscopic left adrenalectomy, and the pathology revealed chronic inflammation. He was totally recovered uneventfully and no adrenal insufficiency developed during follow-up. Adrenal infection is a rare cause of adrenal disorder in adults. The adrenal gland can be infected by a myriad of pathogens, and Mycobacterium tuberculosis was the most common causative agent. Streptococcus constellatus infection was likely cause abscess, but no report as adrenal abscess. Immunocompromised individuals are at greatest risk for adrenal infection. Antibiotic treatment or surgical intervention remains debate.

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AEP79

Endothelial vascular adrenal cyst with unusual presentation

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Primary adrenal cysts are a relatively rare form of lesions with incidence of 0.06% in general population and higher prevalence in women (female-to-male ratio 2.3:1). Adrenal endothelial cysts are the most common form of adrenal cysts subtypes (45%) and they usually present with abdominal or flank pain, or nonspecific symptoms . Adrenocortical carcinomas are a rare condition as well, with an incidence of 1–2 per million per year. The typical clinical presentation may include symptoms of glucocorticoid excess and systemic symptoms such as weight loss, anorexia, leukocytosis, and fever.
We describe a case of a 51-year-old female with poorly controlled hypothyroidism. She presented to endocrinology clinic with a history of fever for three months. The clinical evaluation of fever of unknown origin was unremarkable. A CT scan demonstrated a 3.6×2.6 cm heterogenic mass in the leftadrenal. Endocrine blood tests revealed no abnormalities besides overnight dexamethasone (1 mg) suppression test that demonstrated partial suppression of cortisol levels (126 nmol/l). As malignancy was suspected, the patient was referred to surgery and the adrenal was removed laparoscopically. Surprisingly, histology confirmed endothelial/vascular cyst. During multiple follow-up visits over a period of 18 months, the fever has completely resolved. This demonstrates the first known case of endothelial/vascular adrenal cyst presenting with persistent fever.

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AEP80

Less common form of adult secondary hypertension

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Introduction
Patients with clinical clues suggesting the possible presence of secondary hypertension should undergo a more extensive evaluation, because in this case some of these disorders can be cured, leading to partial or complete normalization of the blood pressure.
Case description
We report a case of a 43-year-old man, who suffered for years of hypertension despite concurrent use of adequate doses of three antihypertensive agents from different classes. He presented a heart failure, diffuse hypokinesia and a reduction of his ejection fraction to 40%. In the blood tests he had hypokalemia, low cortisol (117 mmol/l) with high ACTH (1013 ng/l), low aldosterone (21.8 ng/l) and renin at 9 µUI/ml. In this context we tested testosterone (30.4 nmol/l), androstenedione (31 ng/ml), DHEAS (17,8 µmol), 17OH progesterone (8 ng/ml) and the 11 deoxycortisol (>30 ng/ml). The abdominal scan showed bilateral adrenal hyperplasia and on testicular ultrasound the patient presented bilateral intra-testicular lesions compatible with intra-testicular adrenal inclusions. The genetic test confirmed the suspicion of the congenital adrenal hyperplasia by 11-hydroxylase deficiency. It showed a homozygous mutation in the CYP11B1 gene, chromosome 8, exon 8, pArg448His. The patient didn't have the adrenal crisis before despite the cortisol deficiency. We started the treatment by Dexamethasone 0.5 mg per day and 6 months later we obtained a normalization of the blood pressure and a decrease of adrenals hyperplasia and intra-testicular adrenal inclusions.
Discussions
CYP11B1 deficiency affects 1 in 100,000 live births and accounts for up to 5% of adrenal steroidogenic defects. The frequency of no classic disease is far less common for 11hydroxylase. Patients do not have adrenal crisis due to accumulated adrenal steroid precursors that can activate the glucocorticoid receptors, especially for hydroxylation at position 11 which enhances glucocorticoid activity.
Conclusions
We report a case with a late diagnostic of congenital adrenal hyperplasia by 11-hydroxylase deficiency, with proven cortisol deficiency without adrenal crisis, but good treatment response.
Keywords: hypertension, congenital adrenal hyperplasia, 11-hydroxylase deficiency
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AEP81

Behavior of adrenal incidentalomas with density computed tomography scan > 10 HU

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Background
The prevalence of adrenal incidentalomas has increased. The malignancy is determined by radiographic appearance and, secondly, by the size. Adenomas manifest a low attenuation on computed tomography (CT) (<10 Hounsfield Units(HU)).The cut-off point of 10 HU has been proposed to discriminate benign and malignant lesions.
Objective
To determine if the cut-off point of 10 HU is useful in clinical practice to discriminate benign and malignant incidentalomas. Determine if there are other discriminatory characteristics.
Methods
Retrospective serie of patients referred for adrenal incidentaloma in imaging test between 2015–2019.The characteristics of incidentalomas by CT and other tests were evaluated and associated with the final diagnosis.
Results
Baseline characteristics are shown in Table 1. Of the 139 patients,3 were diagnosed of adenoma by magnetic resonance (MR). In the remaining 136,CT without contrast was performed and the results are shown in Table 2. Of the 27 lesions with CT>10 HU:9 were adenomas (false negatives of CT), 9 other diagnosis and 10 were lesions with uncertain malignant potential (UMP).
Finally, 8 patients (6%) were operated: 3 functioning adenomas and the rest corresponding to the UMP group: 1 pheochromocytoma (17UH), 1 hematoma (16UH), 1 cyst (>10UH), 1 metastasis (22UH) and 1 bleeding adenoma(>10UH). Of the 5 that were not operated,2 died during follow-up,1 decided not to continue the study and 2 are keeping under observation by PET-CT without hypermetabolism. No differences were observed depending on the size between the different lesions. Finally, there were 116 adrenal adenomas:12% were false negatives on CT without contrast using a 10 HU cut-off point. The sensitivity to detect adenomas was 88%.
Conclusions
CT without contrast is an adequate tool to typify adrenal lesions and confirm or rule out malignancy.
The 10 HU cut-off pointdiscriminates properly benign lesions from malignant/uncertain behavior.
The size was not discriminatory to differentiate benign or malignant lesions.
It should be considered not to request metanephrines in patients with a characteristic image of adenoma on CT because image's diagnosis excludes that of pheochromocytoma.

Table 1

Baseline characteristics	N(%)
Sex:	
Man	54 (38,8)
Age(years)	65.4 +/- 11,5
Initial test:	
CT without contrast	37(26,6)
MR	8(5,8)
CT with contrast	87(62,6)
Ecography	5(3,6)
PET-TC	2(1,4)
Size(mm)	24,24+/-11,64

Table 2

HU	Initial CT		Total	Diagnosis
	Confirms adenoma	Not confirm adenoma		
Typical(<10)	98	0	98	-Adenoma 91 -Hyperplasia 7
Not typical(>10)	0	27	27	-Adenomas 8 -Pheocromocytoma 1 -Myelolipoma 4 -Hematoma 1 -Cyst 1 -Hyperplasia 1 -Metastasis 1 -UMP 10
HU negative	0	3	3	-Myelolipoma 2 -Adenoma 1
Not found	4	4	8	-Adenoma 5 -Hyperplasia 3

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AEP82

Malignant collision tumour in left adrenal gland- A rare tumour

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We present a 41 years old lady who presented with non specifc symptoms-lethargy, general myalgia, memory impairment. She also complained of hot flushes, sweats and had a brief episode of panic attacks hence was commence on Sertraline by the GP. She has a past medical history of appendicectomy. Her mother had lymphoma and mother died from lung cancer. She is a smoker, however is teetotal. She has 3 children and works in a laundry. She was initially referred to the haematologist for investigation of lympho-

cytosis and neutrophiliawho subsequently discovered a 51mm left adrenal mass (not typical of an adenoma) raising the possibility of a phaeochromocytoma or adrenal cortical carcinoma through a CT scan subsequently characterised byfurther MRI scans. On clinical examination, her blood pressure was 126/73 sitting and 125/84 standing with a regular pulse of 82bpm. She has no cushingoid features and no proximal myopathy. Her investigations showed a normal cortisol 18 nmol/l post overnight dexamethasone suppression test. Raised Metanephrines 6.8 umol/24 h (0-3 umol/24 hr), Raised Normetanepherine 7.35 umol/24 h (0-1.14 umol/24 h), 3-methoxytyramine 2.11 umol/24 h Normal. Aldosterone renin ratio, DHEA 3.70 umol/l normal, Aldosterone renin ratio 25.3 pmol/mU Normal She was alpha and beta blocked prior to surgery. She had a left laparoscopic adrenalectomy where her histology results showed a mixed composite of phaeochromcytoma/paraganglioma with neuroblastic elements. Immunohistochemistry showed some areas staining strongly with chromogranin and synaptophysin while other areas are weaker. The Ki67 proliferation index is <1%. Post operatively, she had a 123I-mIBG scintigraphy scan which show physiological tracer distribution with no abnormal focal mIBG avidity. She consented for genetic testing and undergone the pheochromocytoma and paraganglioma gene paneltesting (FH, MAX, RET exons 10&11, SDHA, SDHAF1, SDHB, SDHC, SDHD, TMEM127, VHL) with no alteration identified. Her RET gene testing (exons 5, 8, 10, 11, 13, 14, 15 and 16) is also normal. She was offered entry into the molecular pathology of human genetic diseasese Post operatively, she recovered well, her subsequent 24 hour metanephrines normalised. Serial CT scans show no disease recurrence so far. Adjuvant chemotherapy was also discussed with the oncology team. However, this wasn't deemed necessary and surveillance was advocated. This is a very rare tumour with few case series reported. This case adds to the sparse literature on this type of tumour and uncertainties regarding longterm management.

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AEP83

JIL-O: Establishment of a new steroidogenic human adrenocortical carcinoma cell line

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Adrenocortical carcinoma (ACC) is a rare malignancy with heterogeneous but dismal prognosis and despite numerous efforts to improve patient care, effective treatment options are still lacking. ACC *in vitro* research faces for decades one major obstacle - the unavailability of different ACC cell line models. Here, we present a newly established human ACC cell line that was directly transferred to and now proliferates in cell culture. JIL-O cell line was derived from a primary adrenal tumor of a female, fifty-year-old patient with ENSAT stage IV. The patient presented with clinical symptoms of hypercortisolism and androgen excess and was treatment-naïve at the time of surgery. Subsequently, she received palliative mitotane and cytotoxic chemotherapy. Short tandem repeat (STR) profiling confirmed matches between the tumour and the derived cell line. Both tumour tissue and JIL-O cells were exome sequenced and a hemizygous TP53 mutation (NM_000546.5: c.859G>T: p.Glu287*) in the cell line excluded contamination with healthy cells. JIL-O cells stained positive for steroidogenic factor 1 (SF-1) by western blot. Hormone profile panels were determined by LC-MS/MS and those of the cell line matched to the secretion of the tumour in the patient, withexcessive secretion of cortisol, 11-deoxycortisol and androgens (androstendione, DHEA, testosterone). JIL-O cells adhere on plastic and started to proliferate after being in cell culture for more than one year with a doubling time of approximately 39 hours. To our knowledge, this is the first ACC cell line since the establishment of the NCI-H295R cell line that was directly transferred into *in vitro* culture without implantation into mice. JIL-O cells hence present another new tool to study ACC *in vitro* and hopefully help to reflect heterogeneity of this rare malignancy.

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AEP84

Prognostic factors and overall survival in patients with adrenocortical cancer: Experiences of a single tertiary referral endocrine centre in Hungary (1974–2019)

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Introduction
Adrenocortical cancer is a rare malignant tumour with a poor prognosis. The incidence is 0.7–2.0/million/year.
Objectives
The aim of this study was to characterise the clinicopathological features and prognostic factors of a large cohort of patients with adrenocortical cancer diagnosed between 1974–2019.
Patients and methods
The study included eighty patients (22 men and 58 women) with histologically confirmed adrenocortical cancer in our single tertiary referral endocrine unit. Sixty-two and forty-three of the patients were diagnosed after years 2000 and 2010, resp. Descriptive statistics were performed, providing summaries of selected clinical and pathological parameters at the time of diagnosis. The results are given in median (minimum-maximum). Factors contributing to overall survival were analysed. A p value of less than 0.05 was considered statistically significant.
Results
The median age of patients was 52 years (18–84 years) at diagnosis. The majority of cases was diagnosed at ENSAT stage II (41.4%) and stage IV (34.3%), the median tumour size was 9.5 cm (4–30 cm) at diagnosis. In 57 patients (76%) the tumour was hormonally active. Primary surgical tumour resection was performed in 70 patients (87.5%), in 30 patients R0 resection was achieved. The median overall survival and the 5-year survival rate were 23 months (0–274 months) and 20%, respectively. In univariate Cox regression model, older age (>57 years), tumours with stage III-IV, high mitotic activity of the tumour cells (Ki67-index >20%) and R1-R2 surgical resection state were associated with poorer survival. The overall survival of patients achieving therapeutic mitotane plasma concentration ($n=21$) was significantly better comparing to those who failed to achieve the therapeutic serum mitotane concentration ($n=22$) (38 (13–193) months vs 18 (2–101) months). The time needed to reach the therapeutic range of serum mitotane was 4 (2–12) months. The median age, the distribution of gender, ENSAT stage, resection stage and Ki67-index stratified to 20% did not differ between these two groups. In patients with stage III-IV disease, there was no significant difference in overall survival between those who were treated with mitotane monotherapy compared to those with combined (mitotane plus chemo- therapy (19 (2–193) months, $n=8$ vs 18.5 (4–76) months, $n=18$).
Conclusion
Our results confirmprevious data that age, disease stage, mitotic activity and the resection stage are the most critical factors influencing the prognosis of adrenocortical cancer. The rapid achievement of therapeutic mitotane concentration has a significant and independent effect on overall survival.

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AEP85

The effect of surgeon's experience on the outcome of patients with ACC

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Introduction
Adrenocortical carcinoma (ACC)is a rare disease with an unfavourable prognosis. Complete surgical resection of the tumour provides the only chance for long-term cure. The aim of this study was to compare long term outcomes in patients with ACC referred to surgery in an expert adrenal centre (EC) versus nonspecialised centres (NSC).
Materials and methods
This retrospective study included 48 patients with ACC, ENSAT stage I-III. All of study participants underwent complete tumour resection of whom 35 (73%) were operated in a high-volume centre by a dedicated surgeon, whereas 13 (27%) patients were operated in nonspecialised centres. The study analysed the differences between the two groups in terms of recurrence free survival (RFS) and overall survival (OS).
Results
Median duration of follow-up was 51 months (5–174) in EC group and 46 months (3–165) in NSC group. Disease recurrence was observed in 5 (14.3%) patients in the EC group and in 5 (38.5%) patients in the NSC group ($P=0.067$). Patients in the EC group had longer PFS but the difference did not reached the level of statistical significance (28 (11–45) month vs 19 (3–43) months; $P=0.083$). Overall, seven patients died during follow-up (5 EC, 2 NSC). ACC was the cause of death in two EC patients (5.7%) and in two NSC patients (15.4%; $P=0.16$).
Conclusion
The above-mentioned results show thatACC recurrence is less likely to occur in patients operated by a dedicated surgeon in an expert adrenal centre.

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AEP86

VDR-GR complex reduces apoptosis in acute myeloid leukemia cells via reduction of GR transcriptional activity

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Introduction
Glucocroticoids (GCs) which are routinely used in the treatment of Acute Lymphocytic Leukemia (ALL), found recently to be beneficial in a subset of AML patients resistant to chemotherapy, by promoting leukemia cells apoptosis. Current studies indicate that vitamin D (VitD) deficiency is highly prevalent among AML patients, posing vitamin D as a therapeutic supplementation. Our previous study demonstrated that VitD exerts inhibitory effect on Dexamethasone-induced apoptosis in AML cells via altering Bcl2/Bax ratio, and inhibits GC-mediated cell cycle arrest through reduction of p21.
Aim
In the present study, we aimed to clarify if 1) these actions are mediated through formation of GR-VDR complex and 2) this complex is driven by VitD (1,25 (OH)2D3) in the promoter of Bax and p21 or not.
Methods
Kasumi-1 cells were incubated for 72 hours with dexamethasone (Dex-10–6M and 10–7M) alone or pre-incubated with VitD (10–8M) for 24 h following by co-incubation with Dex. MTS assay was performed to quantify viable cells whereas apoptosis was evaluated by Annexin V/PI based flow-cytometry assay. The mRNA levels of apoptotic and anti-apoptotic markers such as Mcl-1, Noxa, Bcl-2, Bax, p21 was measured by quantitative real time PCR. Immunoprecipitation was performed in order to examine the formation of GR-VDR complex, while ChIP assay was employed in order to evaluate GR-VDR occupancy at the Bax and p21 promoters.
Results
MTS and FACS analysis indicated that Dex induces apoptosis in Kasumi-1 cells dose-dependetly, while this effect was reduced significantly when cells were pre-incubated with VitD. Bax and p21 mRNA expression was significantly decreased in cells pre-incubated with VitD (24h) following by co-incubation with Dex for further 72 h as compared to cells incubated with Dex alone. Immunoprecipitation showed that GR forms a stable complex with VDR in cells preicubated with VitD . Moreover, ChIP analysis showed that preincubation with VitD increased the formation ofGR-VDR complex. Additionally, pre-incubation ofcells with vitamin D decreased the binding of this complex in p21 promoter.
Conclusions
VitD inhibits Dex induced-apoptosis and induces cell survival in AML cells, at least in part, via formation of VDR-GR complex and attenuation of GR transcriptional activity.

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AEP87

Cortisol response to acute stress is dependent on previous stress exposure and sex of the examined humans

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Introduction
Prolonged exposure to stress has a modifying effect on activity of hypothalamo-pituitary-adrenal (HPA) axis. This is a protective adaptation aimed to diminish potential deleterious effects of chronic hypercortisolism, and to diminish effects of acute exposure to heterotypic forms of stress. Our aim was to analyze modes of cortisol response to acute physical stress in groups of different stress categories and sex.
Subjects and methods
Study group consisted of 17 healthy males (23 ± 1 years old) exposed to current psychological stress (medical students during exams) – SM (stressed males). Two age matched control groups were: 1) 20 males (22 ± 3 years old) currently not exposed to stress – NSM (nonstressed males), and 2) 17 females (23 ± 2 years old) currently exposed to psychological stress (medical students during exams) – SF (stressed females). All subjects were exposed to acute physical stress by performing cardiopulmonary exercise test on a treadmill. Cortisol response was measured at 4time points: B at baseline (during rest), S at the start of the test (the moment of stepping on a treadmill), and MAX at the point of maximal effort, and R at the 3rd minute of recovery period. Statistical analysis was performed using SPSS software. Specifically, ANOVA for repeated measures was used to analyze difference in cortisol response during stress test.
Results
Stressed males had significantly higher cortisol levels than NSM at all time points ($P<0.001$, $P<0.001$, $P=0.007$, $P=0.015$ for B, S, MAX and R respectively), but the pattern of response was significantly different ($F_{1}=9.75$, $P=0.004$); SM had attenuated cortisol response compared to NSM, with significantly smaller percent of change between S and MAX ($P=0.04$) and between MAX and R ($P=0.039$). Similarly, cortisol was higher in SM than in SF ($P=0.004$, $P=0.002$, $P=0.001$ and $P=0.001$, for B, S, MAX and R respectively), but the pattern of stress response was similar ($F_{2,1}=1.605$, $P=0.208$). Stressed females had higher baseline cortisol levels than NSM ($P=0.015$), but the difference was lost throughout the test ($P=0.125$, $P=0.752$, and $P=0.283$, for S, MAX and R respectively). This was due to a fact that NSM had a more pronounced cortisol response compared to SF ($F_{1,9}=13.649$, $P<0.001$), with significantly greater percent of change between P and MAX ($P=0.001$) and MAX and R ($P=0.039$).
Conclusion
Lasting psychological stress exposure modifies the pattern of acute cortisol response to physical stress, but overall HPA axis activity is strongly dependent on the sex of examined subjects.

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AEP88

Investigating differences regarding stress hormonal response during vaginal delivery and elective caesarean section

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Introduction
Despite the fact that CS is widely employed, further investigation on the topic of the physiology vis a vis this type of delivery is required, especially regardingstress related hormonal response during this practice. The aim of this study is to provide data regarding stress related hormonal response during Vaginal Delivery (VD) and elective CS evaluating levels of Cortisol, Interleukin 6 (IL-6), Growth Hormone (GH) and Insulin-like Growth Factor 1 (IGF-1).
Materials and methods
The sample size of this study ($n=50$) was divided in two groups, namely the VD ($n=26$) and the CS ($n=24$)groups. The inclusion criteria were the following: healthy women aged 20–43 years, with hitherto uncomplicated singleton pregnancies who underwent spontaneous VD or elective CS, at a gestational age ranging from 37–40 weeks. Peripheral blood samples were collected at three different time-points. Time-Point 1 (TP1): samples collected at the first stage of labor for VD or 30 minutes following admission to the hospital for CS. Time-Point 2 (TP2): samples collected 120 minutes following placenta delivery. Time-Point 3 (TP3): samples collected 48 hours following placenta delivery. Umbilical cord blood samples were collected following placenta delivery. Evaluation of hormonal levels were performedvia standard ELISA.
Results
No significant difference could be established between the two groups regarding all hormones in the TP1. Cortisol levels did not differ at TP3 between the VDG and the CSG. The CSG presented with lower levels compared to the VDG (129.93 ± 63.10 vs 299.58 ± 74.00, P-value <0.001) at TP2. IL-6 levels were lower in the CSG at TP2 (20.15 ± 7.25 vs 48.70 ± 7.45, P -value <0.001) and higher at TP3 (21.85 ± 6.35 vs 6.86 ± 5.86, P –value <0.001) compared to the VDG. IGF-1 levels were higher at TP2 in the CSG (230 ± 80.63 vs 173.15 ± 38.12, P -value $=0.004$) in comparison to VDG, but were similar between the two groups at TP3 (101.38 ± 80.63 vs 88.19 ± 18.89, P -value $=0.94$). Cortisol and IL-6 levels in the umbilical blood did not present with a statistically significant difference between the two groups. IGF-1 and GH levels in the umbilical blood were statistically significantly higher in the CSG.
Conclusion
Data presented indicate that CS is a less stressful procedure for mothers in comparison to VD, and is further associated with less intense inflammation with an albeit longer inflammatory response period. From the infants' perspective, GH and IGF-1 appear to be increased in the umbilical cord blood of CS born neonates. Nonetheless, whether this may be attributed to mode of delivery remains unanswered.

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AEP89

Apparent mineralocorticoid excess (AME): Finding the "root" cause

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Liquorice is a sweetener found in many food products, soft drinks, snacks and herbal medicines. Liquorice ingestion is an uncommon cause of AME or pseudohyperaldosteronisim. The mechanism involves the inhibition of 11-beta-hydroxysteroid dehydrogenase type-2 by the active ingredient called glycyrrhizin, which leads to the uninhibited activation of mineralocorticoid receptors by cortisol. Confectionary products that contain liquorice are readily available in the European Union.
We report a case of severe refractory hypokalaemia due to excessive liquorice consumption. A 79-year-old female presented to the emergency department following a road traffic accident secondary to collapse. She described feeling weak in the preceding weeks and was managed by her GP for hypokalaemia. Investigations revealed hypertension (BP 180/69 mmHg), severe hypokalaemia (K 2.2 mmol/l), normal renal function (Na 143 mmol/l, urea 3.4 mmol/l, creatinine 54 umol/l), normal magnesium (0.79 mmol/l) and calcium (2.24 mmol/l) levels with metabolic alkalosis (pH 7.537, bicarbonate 33.5 mmol/l). Spot urinary potassium was 22 mmol/l. The patient denied taking medications including over-the-counter or herbal medicines that can cause hypokalaemia. Hypokalaemia persisted for six days despite aggressive IV and oral potassium replacement. She later developed hypertensive emergency (BP 239/114 mmHg) with pulmonary oedema and required admission to intensive care unit for emergency management of hypertension with intravenous furosemide infusion and isosorbide dinitrate infusion. Further discussion with the patient revealed that since she quitted smoking, she was taking liquorice sweets excessively for the past 3 months to manage her nicotine cravings. Suppression of plasma renin [4.4 pg/ml (reference range <20 pg/ml)] and aldosterone levels [<26 pg/ml (reference range 42–209 pg/ml)] also supported the diagnosis of AME. Her symptoms and hypokalaemia resolved since discontinuing liquorice. This case highlights the life-threatening and refractory nature of severe hypokalaemia and hypertensive emergency caused by pseudohyperaldosteronisim secondary to excessive liquorice consumption. This case also emphasizes the importance of comprehensive history taking including the dietary habits to identify the root cause. Increased awareness among the public is required regarding the potential health hazards of excessive liquorice consumption.

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AEP90

Hypertensive crises related to the defecation strain, what's the diagnosis?

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Introduction
The defecatory strain in constipated people can raise the blood pressure and occasionally trigger cardiovascular events.
Methods
Review of the patient's clinical records and the relevant literature.
Results
Clinical Case: A 53-year old woman with history of breast surgery for adenocarcinoma and chronical constipation had severe resistant hypertension in the previous three years; she had hypertensive crises with SBP up to 260 mmHg with headache but no vegetative symptoms; often these crises had been elicited by the defecation strain. In a extension study five years after breast surgery the CT showed a heterogeneous, dense (mean density 110 UH) right adrenal mass measuring 39–43 mm suggestive of metastasis; she was referred to our Hypertension Clinic for evaluation. Under treatment with amlodipine and doxazosine lab tests were obtained, with normal cortisol, ACTH, LH, FSH, aldosterone, renin activity and A/RA ratio (10.5); plasma metanephrine was 104 pg/ml and normetanephrine >2400 pg/ml. A 125-I-MIBG SPECT-CT showed intense activity in the right adrenal without additional findings. After routine presurgical preparation with doxazosine followed by bisoprolol, a 24 h ABPM was performed showing a diurnal mean BP of 127/65 mmHg, HR 87 bpm, and nocturnal 120/64 mmHg, HR 83 bpm (non- dipper) without any SBP data >130 except for a peak (148/76 mmHg) at 21:34 coincident with strained defecation. The right adrenal was laparoscopically removed without complications. The pathology diagnosis was a 6 cm pheochromocytoma without apparent malignancy (Ki-67 <2%). After the surgery the patient remains normotensive without medication and her plasma metanephrines are normal (32/64 pg/ml) but remains constipated.
Conclusions
The defecation strain associated to chronic constipation might squeeze a large non-metastatic pheochromocytoma and cause hypertensive crises. Although raised blood pressure in connection with constipation has often been reported, the triggering of hypertensive crises by defecation strain in a patient with pheochromocytoma had not been previously reported in our knowledge.

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AEP91

Composite pheochromocytoma of the adrenal gland: Case report

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Introduction
Composite pheochromocytoma is a rare tumor composed histologically of pheochromocytoma and other neurogenic tumor components such as neuroblastoma, ganglioneuroblastoma, ganglioneuroma, peripheral nerve sheath tumor, or other types of neuroendocrine carcinoma. The frequency of composite adrenal tumors reportedly ranges from <3% of all adrenal gland neoplasms to 1–9% of pheochromocytomas. The clinicopathological diagnosis of composite pheochromocytoma is, at times, a clinical dilemma because it is not known whether the nonpheochromocytoma component has any therapeutic and/or prognostic implications as compared to the standard pheochromocytoma.
Case report
A 82-year-old male presented with gastrointestinal complaints (abdominal pain and diarrhea) for 2 months along with facial flushing, sweating and 10 kg weight loss. He had a history of mild hypertension with orthostatic hypotension. Hemogram reports revealed anemia. Abdominal ultrasonography and computed tomography showed the presence of a large heterogeneous mass 118×135×108 mm with well-defined boundaries in the left suprarenal region. In view of adrenal tumors, 24-hr urinary metanephrine was further evaluated, with high levels 1674,17 mg/24-hrs (reference range, 25–312), plasma free metanephrines levels: 707,5 ng/l (reference range, 7,9-88,7), cortisol level was 1,76 ug/dl after overnight dexamethasone suppression test showed normal suppression, plasma level of chromogranin A was 746,3 ng/ml (reference range <76,3). Left adrenalectomy was performed. The anesthetic team confronted with intraoperative complications: arrhythmia. Postoperative period was uneventful and plasma levels of free metanephrines and normetanephrines normalized: 74,8pg/ml (reference range, <65), respectively148,1 pg/ml (reference range, <196). Pathological diagnosis was composite pheochromocytoma / ganglioneuroma.
Conclusions
Composite pheochromocytomas are rare catecholamine-producing tumor which has the propensity to large size which is unlikely when it is classical pheochromocytoma. Clinical manifestations unique to the tumor are occasional and atypical and non-specific symptomatology and its association with autoimmune disorders. A multidisciplinary approach involving anesthesia, endocrinology, and surgical expertise is the gold standard in maximizing patient care.

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AEP92

Cystic pheochromocytoma, a diagnostic challenge: A case report

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We describe a case of cystic pheochromocytoma (PCC) with negative biochemical evaluation, diagnosed on the basis of hypertensive crises during operative management and histopathologic findings. A 57-year-old woman complained of several episodes of stabbing right upper abdominal pain accompanied by tachycardia, headache, lack of breath, elevated blood pressure and vomiting in the preceding three years. At presentation, blood investigations were significant only for mildly elevated transaminases and serum amylase. An abdominal ultrasound was performed and revealed large right adrenal incapsulated and heterogenous mass, 7×7 cm in size, with mass effect. Computed tomography imaging confirmed incapsulated adrenal mass with internal septations and unenhanced attenuation of >30 Hounsfield units. Based on imaging appearance and patient's history, a suspicion of PCC was established, and the patient was referred to endocrinologist. Laboratory exams for Cushing's syndrome were unremarkable and urinary vanilmandelic acid, metanephrines and serum chromorgranin A were within normal range on several occasions. Further evaluation with iodine-123 (123I)-labeled metaiodobenzylguanidine (MIBG) scintigraphy would have been useful to differentiate the mass, but it was not available at the moment of investigations. Despite negative biochemical diagnosis,strong clinical suspicion for PCC was established and the patient was preoperatively prepared with α-adrenoreceptor and beta blockers. Initial attempt for laparoscopic adrenelectomy was unsuccessful due to early intraoperative occurrence ofhypertensive crises with blood pressure 300/150 mmHg. Three months later a successful open adrenelectomy was performed with nonsignificant intraoperative hemodynamic instability. Histopathologic evaluationconfirmed cystic benign PCC with dominance of multnuclear giant, foamy macrophages, presence of hemosiderin deposition and hemolyzed erythrocytes. Although cystic adrenal lesions comprise several types of non-functionating benign lesions, the differential diagnosis should include cystic form of PCC, an entity that is rarely reported. In cystic PCC the number of cateholamin-producing cells are low, especially when an extensive necrotic cystic regions are present. Furthermore, catecholamines stored in the capsular mass may not be released into the blood circulation until surgical attempt for isolation of PCC is made. Therefore, high clinical suspicion for PCC is necessary since negative biochemical diagnosis is possible. As demonstrated by our case, clinical presentation was crucial in the diagnosis and preoperative management. Preoperative optimization with antihypertensive drugs and blood volume expansion fluids is obligatory in PCC surgery in order to prevent detrimental intraoperative hemodynamic instability. Albeit laparoscopic adrenelectomy is becoming a first line surgical option for PCC, still it's not always feasible as shown in our case.

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AEP93

Type 1 neurofibromatosis and malignant pheochromocytoma

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Introduction
Neurofibromatosis type 1 is a disease caused by mutations in the tumor suppressor gene NF1.
Although pheochromocytoma is a rare manifestation in these patients (~0.1–5.7%), the incidence is significantly higher than that of the general population.
Results (case description)
A 50 years old female patient had a clinical diagnosis of neurofibromatosis type 1 since she was 5 years old. She received follow-up in internal medicine appointments since 1999 after a paroxistic episode of headache, palpitations, dizziness and pre-cordial discomfort in the postpartum period, initially attributed to anxiety. The episodes were repeated in the following years and coincided with hypertensive peaks. In 2002 she was admitted to the hospital, and the complementary diagnosis exams revealed: increase in metanephrines and vanillmandelic acid; heterogeneous nodular formations on the left and on the right adrenal glands(~5.2×4.9 cm and ~5.4×8.9 cm, respectively) in abdominal computerized tomography; bilateral adrenal masses intensely fixating the radiopharmaceutical contrast in the MIBG scintigram. She underwent a bilateral adrenalectomy (after α and β block). The anatomopathological result reported a "bilateral pheochromocytoma" - PASS score 3 on the right and 6 on the left. In the subsequent years, she underwent follow-up in endocrinology and internal medicine appointments at different hospitals, however some appointmentswere missed. In 2015 a chest magnetic resonancerevealed an hyperintense 16×19 mm right-hilar nodular lesion in T1 and T2. Between 2016–2018, slightly elevated metanephrines were detected - maximum metanephrine 185,7 ng/ml (<60) and normetanephrine 247,9 ng/ml (<120). In 2019, DOPA-F18positron emission tomography (PET) revealed right bronchociliary nodular formation with intense DOPA-F18 uptake, suggesting a neuroendocrine tumor /pheochromocytoma ganglion metastasis. The patient underwent excision of the right hilar lesion (after α and β block) and the anatomopathological result reported a pheochromocytoma metastasis, PASS 5 score, ki67 <1%. Currently, sheis under regular clinical, biochemical and imagiological follow-up at the endocrinology department.
Conclusions
Although pheochromocytoma is a rare manifestation of neurofibromatosis type 1, the presence of arterial hypertension in these patients should lead to suspicion of the diagnosis. The hypertensive crisis recorded in the postpartum period was one of the first manifestations of the tumor.
Patients with neurofibromatosis type 1must be monitored regularly by professionals specialized in the various manifestations of the disease. The irregular follow-up of this patient, hindered an adequate evaluation and delayed the diagnosis of metastatic disease.

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AEP94

Results of biochemical testing in suspected primary hyperaldosteronism – a retrospective study

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Background
PA is a frequent cause (5–13%) of secondary hypertension (HT), yet diagnostic work-up of PA remains challenging.
Aim
To describe the characteristics of a series of hypertensive patients diagnosed with PA compared to those with negative biochemical screening (aldosterone-to-renin ratio/ARR)
Methods
Clinical, hormonal and imaging evaluation.
Results
We have screened for PA 34 patients diagnosed with HT, using as screening criteria: 1. HT+hypokaliemia,2. early-onset HT, 3. drug-resistant HT, 4. HT+sleep apnea, 5. HT+adrenal incidentaloma. 15 patients (7M/8F), aged 39.5 yo (17–58, median/range) at HT onset had a diagnosis of PA confirmed by biochemical testing. Twelve patients (80%) with PA and 14 patients (73.7%) with primary HT had stage 3 HT. Systolic and diastolic BP were significantly higher in PA confirmed group (median SBP 140 mmHg vs 125 mmHg and median DBP 90 mmHg vs 80 mmHg). There was a higher prevalence of drug-resistant HT in PA patients (60% vs 10%). Hypokaliemia history was documented in 6 patients (40%) with PA and in 2 patients (10.5%) with primary HT. ARR on RAAS-interfering drugs (ARRon) was 87 (1.04–426.6) in PA group and 17.28 (0.47–63.44) in primary HT group. Repeated ARR after RAAS-interfering drugs discontinuation in 10 patients (ARRoff) was 59.85 (1.21–926). We performed 20 confirmatory tests in 14 patients (17 tests for PA pts and 3 for primary HT pts): 14 saline infusion tests (SIT), 5 captopril challenge tests (CCT) and one oral salt loading. 13 patients were SIT-positive (aldosterone>5 ng/dl), 2 patients were CCT-positive (aldosterone suppression <30%), one CCT-negative patient (2 h suppression = 25.6%) was SIT-positive. Adrenal CT identified unilateral adenomas in 8 patients (53.3%), 5 of whom associated a diffusely enlarged contralateral adrenal. One patient underwent unilateral adrenalectomy and he was biochemically cured, the 14 remaining received mineralocorticoid receptor antagonists. Target organ complications were present in 6 pts with PA (40%) patients: 5 presented cardiomiopathy, 4 had CKD and 3 patients had retinopathy.
Conclusions
PA was a frequent cause of severe secondary HT in our cohort. Systolic and diastolic BP were significantly higher in PA patients compared with those with primary HT and drug-resistant HT prevalence was higher in hypertensive patients with confirmed PA. ARR in patients taking RAAS-interfering medication decreased after drug discontinuation. There were no significantly differences in target organ complications between PA and primary HT patients.
Keywords: primary aldosteronism, aldosterone renin ratio, SIT, CCT
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AEP95

Body composition, insulin sensitivity and blood pressure in patients with congenital adrenal hyperplasia

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Introduction
Management of patientswith congenital adrenal hyperplasia (CAH) is a challenge to find a right balance of glucocorticoid doses and long-term consequences of overtreatment isassociated with increased risk of cardiometabolic disorders.

The aim of our study was to evaluate body mass index (BMI), body composition, blood pressure (BP) and insulin sensitivity in children and youth with CAH in comparison with healthy control subjects.
Methods
Data from 29 patients with CAH (13 males; median age 16.9 ± 6.8, years (10.2–30.9)) were collected retrospectively and compared to 29 healthy controls (14 males; median age 20.2 ± 0.9 years (17.7–21.3), $P = 0.13$). 21 patient had salt-wasting (SW 11 males) and 8 patients - simple virilising (SV, 71 male) form of CAH. Median dose of hydrocortisone (HC) was calculated from CAH diagnosis until last examination. Prednisolone and dexamethasone doses were converted to equivalent HC doses in mg/m^2 per day using standard GC equivalencies (20 mg of HC = 5 mg of prednisolone = 0.4 mg of dexamethasone). Body composition was evaluated in both groups with DXA (Hologic Inc., Bedford, MA, USA). Hypertension was defined as BP >95 percentile in children and adolescents and >140/90 mmHg in adults). Comparisons between two groups were adjusted for age, gender and height. Oral glucose tolerance test (OGTT) was performed and fasting insulin level were evaluated in the CAH group. Insulin sensitivity was determined using homeostasis model assessment of insulin resistance index (HOMA-IR).
Results
Mean BMI was significantly higher in subjects with CAH (1.18 ± 1.3 SDS and 0.18 ± 1.05 SDS, respectively, $P = 0.002$). Total body fat (TBF) mass Z-score was significantly higher in CAH patients vs controls (0.629 ± 0.80 vs –0.04 ± 0.76, $P = 0.003$). Mean total daily dose of HC in the SW group was 15.4 ± 2.3 (11.03–21.41) and in the SV group 14.32 ± 1.29 (12.45 – 15.95) mg/m^2 per day, $P = 0.22$. Hypertension was identified in 24.1% of CAH patients (7 SW and 1 SV) and 13.8% ($n = 4$) of controls ($P < 0.0001$). Impaired glucose tolerance was found in 2 CAH patients (13.3 and 30.1 years-old). In the CAH group, significant association was found between HOMA-IR and visceral adipose tissue in grams ($r = 0.636$, $P = 0.011$) and HOMA-IR and waist-to-hip-ratio ($r = 0.543$, $P = 0.045$). HC dose was not related to BMI, TBF, BP or HOMA-IR.
Conclusions
CAH patients had higher BMI, TBF and frequency of hypertension compared to controls. Doses of glucocorticoids were not associated with body composition and BP in CAH patients.
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AEP96

Confirmatory testing of primary aldosteronism with saline infusion test and LC-MS/MS

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Objective
The saline infusion test (SIT) is a standard confirmatory test for primary aldosteronism (PA) and based on impaired aldosterone suppression in PA compared to essential hypertension (EH). In the past, aldosterone was quantified using immunoassays (IA). Due to the more widespread use of liquid chromatography tandem mass spectrometry (LC-MS/MS) in clinical routine, we aimed at a method-specific aldosterone threshold for the diagnosis of PA during SIT and explored the diagnostic utility of other mineralocorticoids and glucocorticoids.
Design
Cohort study of 187 paired SIT samples at a single tertiary endocrine center 2009–2018. Diagnosis of PA ($n = 103$) and EH ($n = 84$) was established based on clinical routine workup without taking LC-MS/MS values into account.
Methods
LC-MS/MS using a commercial steroid panel with a lower limit of quantification for aldosterone of 10 ng/l. Receiver operator characteristics analysis was used to determine method-specific cut-offs.
Results
Aldosterone measured by IA was on average 31 ng/l higher than with LC-MS/MS. Cut-offs were comparable with 64 ng/l for IA (sensitivity: 93%, specificity: 90%, area under the curve (AUC) 0.955) and 69 ng/l for LC-MS/MS (80%, 89%, 0.902). Other steroids did not provide additional diagnostic value.
Conclusions
Quantification of aldosterone with LC-MS/MS and IA yields in comparable SIT-cut-offs for PA. Lower AUC for LC-MS/MS is likely due to the large

spectrum of disease in PA and previous decision making based on IA results. Until data of a prospective trial with clinical endpoints are available, the suggested cut-off can be used in clinical routine.

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AEP97

Clinical and histopathologic phenotype of a single-center patient cohort operated for unilateral primary aldosteronism

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Objective
Clinical and histopathological assessment of a consecutive series of Munich patients operated between 2016 and 2018 for unilateral primary aldosteronism (PA).
Background
Unilateral PA is the most common surgically curable form of hypertension mainly caused by an aldosterone-producing adenomas (APA). Somatic mutations in *KCNJ5, CACNA1D, ATP1A1* or *ATP2B3*drive the aldosterone excess in the majority of APAs. Genetic variants in *CLCN2* have been described in a familial form of PA.
Design and method
The study included 60 surgical adrenal specimens from patients diagnosed with unilateral PA at a single referral center over a 3-year period (2016 to 2018). Clinical and biochemical outcomes were determined according to the PASO criteria. Histopathology of all resected adrenal was assessed by hematoxylin and eosin and aldosterone synthase (CYP11B2) staining. Aldosterone-producing adenomas were genotyped for known somatic mutations by CYP11B2-immunohistochemistry-guided Sanger sequencing of formalin-fixed adrenals or exome sequencing of fresh-frozen tissue.
Results
The cohort (29 males and 31 females) displayed a mean age at surgery of 51 ± 13 years and a median duration of hypertension of 103 [39–171] months. Complete biochemical success after surgery was observed in 84% of 54 patients with follow-up and complete clinical success was achieved in 19% ($n=10$) with a further 57% ($n=31$) displaying significant clinical improvements (partial clinical success). Histopathologic assessment demonstrated an aldosterone-producing adenoma in 78% (47 of 60) with the remaining 13 adrenals showing multiple micronodules or diffuse hyperplasia. In patients with follow-up, complete biochemical success was achieved in 84% of the 43 patients with an aldosterone-producing adenoma compared with 45% of the 11 patients with diffuse hyperplasia or multiple micronodules. Of 40 genotyped aldosterone-producing adenomas, 22 (55%) had a *KCNJ5* mutation, 4 carried mutations in *ATP1A1* and 4 had *CACNA1D* mutations. Exome sequencing of an aldosterone-producing adenoma identified a *CLCN2* variant (encoding a C244Y mutation).
Conclusions
These findings may contribute to a better understanding of the clinical, histopathologic and genetic correlates of the pathophysiology of unilateral PA.

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AEP98

Expression ofestrogen-related receptors andepidermal growth factor receptorin normal adrenal cortex and adrenocortical tumors: A possible role of GPR30 and EGFR in adrenocortical malignancy

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Introduction
The majority of adrenal neoplasms are benign while adrenocortical carcinomas (ACC) are rare with poor prognosis. Previous studies indicated that estrogens play important role in the etiology and progression of adrenocortical tumors. Estrogens exert genomic activities trough the estrogen-receptor (ER) subtypes α and β, while the non-genomic effects are mediated by membrane-bound-G-protein-coupled-ER-30 (GPR30). Although estrogens induce cancer cell proliferation through ERα, ERβ appears to exert a protective effect. In vitro experiments showed that treatment with ERα antagonist as well as GPR30 agonist reduces proliferation in H295R cells. However, data on the expression profile of ERs in normal and human adrenocortical neoplasms are limited.
Epidermal growth factor receptor (EGFR) found to be highly expressed in ACC. The expression of EGFR has been negatively correlated with expression of ER in other cancers, while data regarding the correlation between ERs and EGFR expression in adrenocortical neoplasms are missing.
Aim
We aimed to investigate the expression profile of ERs and EGFR in adrenocortical neoplasms and correlate it with their biological behavior.
Material and methods
Total RNA was extracted from fresh frozen tissue of:eight non functional adenomas (NFA), eight cortisol producing adenomas (CPA), their adjacent normal adrenal tissues (NAC) AND eight adrenocortical carcinoma (ACC). The expression of ERα, ERβ, GPR30 and EGFR genes was evaluated by qPCR. The Immunohistochemistry (IHC) was performed to evaluate the EGFR and GPR30 protein levels.
Results
The expression of both ERα and GPR30 were higher in the CPA as compared to their adjacent normal tissue ($P<0.05$) while there was no significant difference in ERβ and EGFR mRNA levels between CPA, NFA and their adjacent normal tissues. The expression of GPR30 was significantly higher in ACC compared to either NFA or NAC groups ($P<0.05$), and marginally higher in ACC compared to CPA. The expression of ERα and EGFR was higher in ACC compared to either CPA or NFA ($P<0.1$). IHC confirmed the higher expression EGFR in ACC compared to the adrenal benign tumors. A marginal positive correlation between EGFR and GPR30 expression was observed in ACC.
Conclusion
To our knowledge this the first study to evaluate the expression of membrane-bound GPR30 in human adrenocortical neoplasms. Our preliminary data suggest a possible role of GPR30 and EGFR in adrenocortical malignancy, while ERα may play a role in functional adenomas. Further studies with larger number of samplesare required to elucidate the role of ERs and EGFR on the adrenal tumorigenesis.

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AEP99

Assessment of serum adropin concentrations in primary aldosteronism

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Background
Primary aldosteronism constitutes the most common form of hormonal hypertension. However, it is often mistreated and widely underdiagnosed. Despite the great progress in laboratory technics of adrenal diseases, in the field of primary aldosteronism there is still a need for novel biomarkers that would clarify the diagnosis in equivocal cases. Adropin is a newly discovered protein that may play a role in glucose metabolism and the development of cardiovascular diseases connected to endothelial dysfunction. Lower adropin concentrations has been discovered in patients with primary arterial hypertension in comparison to healthy volunteers. No difference has been yet observed between patients with or without target organ damage related to hypertension, which is most pronounced in primary aldosteronism and refractory hypertension.
Objective
The aim of our studywas to evaluate the differences in adropin levels in hypertensive patients depending on their hormonal status.

Methodology
Adropin, aldosterone and renin concentrations from 80 hypertensive patients were analyzed. 20 patients were diagnosed with primary aldosteronism, 60 patients had primary hypertension. From the whole group, 17 patients had refractory hypertension – only 5 of them had primary aldosteronism. 45% of patientswith primary aldosteronism and 51.6% with primary hypertension had glucose metabolism disorders, including type 2 diabetes and pre-diabetes. Adropin was measured by ELISA method.
Results
Median adropin concentrations in primary aldosteronism were not statistically different from primary hypertension group: 33.2 ng/l versus 45.1 ng/l ($P=0.3$). What's interesting, adropin concentrations were the lowest in patients with refractory hypertension (independently of aldosterone secretion status): median 32.1 ng/l comparing to median 58.6 ng/l ($P=0.0545$) in the group of patients with no refractory hypertension. There was significant difference between the youngest patients (under 40 years of age) in comparison to the older population – 1042.8 ng/l versus 34.9 ng/l ($P=0.04$), respectively. Patients with glucose metabolism disorders had lower, but not statistically different, adropin levels versus patients with normal glucose levels – 34.6 vs 240.1 ng/l ($P=0.07$), respectively.
Conclusions
To our knowledge, this is the first study to assess adropin concentrations in primary aldosteronism. Because of the small sample, the role of adropin needs further evaluation in larger population.

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AEP100

Radiological and functional analysis of a cohort of adrenal adenomas

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Aim
A cohort of adrenal incidentalomas which had radiological or histological characteristics in keeping with an adrenal adenoma was analysed in terms of the radiological and functional characteristics.
Methods
A retrospective cross-sectional analysis of a cohort of adrenal adenomas was carried out. Lesions were followed up for a median of 8.2months (IQR 1.4 – 34.6). In the majority of patients (69.95%), the diagnosis of a benign adrenal adenoma was made via an unenhanced CT scan (density of lesion <10HU in keeping with a lipid rich adenoma). In those patients where the adrenal lesion was lipid poor (density >10HU on an unenhanced CT scan) or had a contrast scan in the first instance, the absolute or relative washouts were calculated in 11.0% and 13.5% respectively. MRI was the imaging modality of choice in 1 patient. 3 patients had an adrenalectomy, with histology confirming an adrenocortical adenoma.
Results
209 patients with adrenal adenomas were included. Out of the whole cohort, 111 patients were females (53.1%). The mean age of patients at diagnosis was 62.3 years (± 12.1SD). Left sided lesions were noted to be the commoner lesions, being present in 61.2% and bilateral lesions in 6.2%. The median longest radiological diameter (on CT or MRI) was 19.0 mm (IQR15.0–25.0). During this follow up period, practically no change in size of the adenomas was identified (median change in size 0 mm (IQR 0 – 1).
Morning cortisol following 1mg overnight dexamethasone suppression was >50 nmol/l in 34.2% in keeping with possible autonomous cortisol secretion. 4 out of these patients had cortisol above 138nmol/l in keeping with autonomous cortisol secretion. 0900 h cortisol post ODST correlated positively with age ($P=0.003$) and longest radiological diameter of adenoma ($P<0.001$) and negatively with DHEAS ($P<0.001$). Multiple logistic regression analysis maintained the positive correlation between 9am post ODST cortisol with age (OR 1.066 $P=0.004$) and longest radiological tumour diameter (OR 1.168 $P<0.001$).
A high aldosterone renin ratio was found in 36% of patients. Out of these patients, 22% also had a level of cortisol following overnight dexamethasone suppression of more than 50 nmol/l.
Conclusion
Interesting correlations between biochemical and radiological parameters in patients with adrenal adenomas have been established. The correlation between 0900 h cortisol following the overnight dexamethasone suppression test and age is not documented in the literature.

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AEP101

Aetiological diagnosis of Cushing's syndrome : A trap for the unwary

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Introduction
Cushing's syndrome denotes pathologic hypercortisolism as a result of excessive adrenocorticotropic hormone (ACTH) production or autonomous adrenal production of cortisol according to the ACTH levels. However, 30% of the patients with CS have ACTH levels in the 'grey zone' (5–20 pg/ml), thereby posing a challenge in establishing the aetiological diagnosis.
Case presentation
A 20-year-old woman presented to our departement with the complaint of weight gain, facial plethora and spaniomenorrheaof 6 months duration. There was no previous medical or surgical history, no family history for endocrine disease. On examination, she had facial plethora, moon facies, centripetal obesity and purple striae on the abdomen and the four limbs. The rest of the exam was within normal limits. Investigations showedno suppression of cortisol after low dose dexamethasone confirming hypercortisolism. Early morning ACTH was 17,9 pg/ml. MRI of sella showed lesion on the left side of the pituitary measuring 5 mm. Since the ACTH level was in the gray zone, the dosage was controlled showing a low level (1,1 pg/ml) confirmed by a third ACTH sample (5,38 pg/ml). Computed tomography for adrenal gland showed a left adrenal mass, 4.4 cm in diameter (arrow), with a density of 30 Hounsfield units and a washout of contrast about 62% at 15 minutes. The diagnosis of pituitary ACTH-independent Cushing's syndromewith pituitary incidentaloma was considered. The patient was subjected to surgery. The resected mass measured 5 cm. Histopathological examination was suggestive of adrenocorticaladenoma with modified Weiss score of 2/7.Postoperative hormonal evaluation showed 08:00 hours serum cortisol at 43.6 nmol/l and hydrocortisone supplementation was continued.
Discussion-conclusion
Cushing's syndromeis a challenging disease to diagnose. The most common cause is Cushing's disease accounting for 70–80% of the cases. Adrenal causes contribute 15–20%.The ACTH value of <5 pg/ml is suggestiveof ACTH-independent Cushing's syndrome, while ACTH value of >20 pg/ml is suggestive of ACTH-dependent, and the levels between 5 and 20 pg/ml arein the 'grey zone'. In this case, testsshould be repeated multiple times and clinicians should be cautious about the possibility of technical errors in any measuring systems. The presence of a pituitary microadenoma, if <6 mm in size, may be an incidental finding in this scenario and can be present in 3–27% of the healthy population. Therefore,multiple samplings for ACTH and adrenal imaging should be performed to exclude ACTH-independent CS.

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AEP102

Is glucocorticoid replacement therapy in adrenal insufficiency a risk factor for liver steatosis?

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Introduction
Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease affecting up to 30% of the population in western countries. Previous studies have demonstrated that increased glucocorticoid levels play an important role in the development of obesity, hyperglycemia, dyslipidemia, insulin resistance, as well as NAFLD. However, the effects of glucocorticoid substitution on the liver in patients with primary or secondary adrenal insufficiency have been rarely examined.
Objective
To investigate the impact of glucocorticoid replacement therapy in patients with primary or secondary adrenal insufficiency on developing NAFLD or liver fibrosis
Methods
Association between the grade of hepatic steatosis and the dose of hydrocortisone replacement therapy was investigated in $n=96$ patients suffering from primary or secondary adrenal insufficiency. The grade of liver steatosis was determined by using an ultrasound-based vibration-controlled transient elastography device called controlled attenuation parameter (CAP). CAP was adjusted for body weight, body mass index and waist circumference.

Additionally, we examined the association between HOMA-Index, hypertension, hyperglycemia and dyslipidemia and the dose of glucocorticoid replacement therapy.
Results
There was no significant correlation between the grade of liver steatosis measured with CAP and the daily dose of glucocorticoid replacement therapy. There was also no significant correlation between the CAP value and the product from the duration of glucocorticoid intake in years and the daily dose of glucocorticoid replacement in mg hydrocortisone equivalent as a marker for cumulative glucocorticoid dose. However, CAP showed a strong correlation with waist circumference ($P<0.001$), BMI ($P<0.001$) and body weight ($P<0.001$). There was a moderate relationship between CAP and the metabolic syndrome ($P<0.001$), hypertension ($P=0.031$) and the level of triglycerides ($P=0.008$). On multiple regression analysis, only waist circumference ($P<0.001$) and dyslipidemia ($P=0.012$) remained significantly associated with CAP. HOMA-Index, hypertension, hyperglycemia and dyslipidemia showed no association with the dose of glucocorticoid replacement therapy.
Conclusion
Glucocorticoid replacement therapy in a physiological daily dose of 15 mg to 30 mg hydrocortisone equivalent seams not to raise the risk of developing NAFLD. Patients suffering from liver steatosis mostly have metabolic risk factors such as obesity, dyslipidemia or hypertension.

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AEP103

Evaluation of clinical and functional differences between unilateral and bilateral adrenal incidentalomas. A spanish multicentric study.

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Purpose
To evaluate differences in the prevalence of autonomous cortisol secretion (ACS) and related comorbidities between patients with unilateral and bilateral adrenal incidentalomas (AI).
Methods
Seven Spanish institutions participated in this institutional review board-approved retrospective study for patients with AI. 342 patients with one or more AI ≥1 cm evaluated by participating physicians between 2001 and 2019 were subject to inclusion. Patients with adrenal lesion detected in the study of extension of an extra-adrenal cancer, with predisposing adrenal hereditary syndromes, manifest functioning AI or missing values in the 1mg dexamethasone suppression test (DST) were excluded. ACS was defined as lack of cortisol suppression after DST in the absence of Cushing Syndrome data. Different cortisol DST thresholds were evaluated: 1.8, 3.0, and 5.0 µg/dl. Diabetes, hypertension, dyslipidemia, cardiovascular and cerebrovascular disease, and obesity were considered ACS related comorbidities.
Results
A total of 256 patients (155 females, 60.6%) were enrolled in the study. 209 (81.6%) had unilateral and 47 (18.4%) bilateral AI. Prevalence of ACS using 1.8 µg/dl, 3.0 µg/dl and 5.0 µg/dl DST threshold was 40.6%, 18.8% and 9.4%, respectively. The prevalence of ACS was significantly higher for bilateral AI (3.0 µg/dl) (31.9% vs 15.8%, $P=0.010$). Bilateral ACS AI presented higher risk of diabetes vs unilateral ACS AI (53.3 vs 18.2%, $P=0.013$) (3.0 µg/dl) and of obesity (71.4% vs 29.4%, $P=0.058$) (5.0 µg/dl). ACS (1.8 µg/dl) was associated with diabetes (OR=1.8, 95% CI=1.01–3.13) and cerebrovascular disease (5.0 µg/dl) (OR=5.3, 95% CI=1.24–22.78) but not with other comorbidities regardless of DST threshold. Patients with ACS (1.8 µg/dl) had lower DHEAS (54.9 vs 121.7 µg/dl, $P=0.009$) and ACTH levels (13.9 vs 21.8 pg/ml, $P=0.001$); higher 24-hour urinary free cortisol (77.5 vs 45.3 µg/24 h, $P=0.056$) and were larger (25.0 vs 20.0 mm, $P=0.002$). Tumor size was negatively correlated with DHEAS ($r_2=-0.16$, $P=0.051$); and positively with DST ($r_2=0.18$, $P=0.014$). However, no analytical or radiological differences were found between bilateral and unilateral AI ($P>0.05$), except for DHEAS (162.0 vs 78.6 µg/dl, $P=0.009$). During follow-up (mean=57.9 months), 6 (6.7%) AI grew (>10 mm); 3 (2.0%) non-functioning AI developed ACS (1.8 µg/dl); and 18.4% developed new comorbidities, being significantly more frequent in patients with ACS (1.8 µg/dl) (28.9% in ACS vs 11.2% in non-functioning, $P<0.001$). Bilaterality was not associated with tumor growth, or development of ACS or comorbidities.
Conclusion
We found higher prevalence of ACS in bilateral compared to unilateral AI, and an increased risk of diabetes and obesity in AI, but not of growth or development of new comorbidities during follow-up.

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AEP104

How innocent are nonfunctioning adrenal incidentalomas?

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Context
Adrenal incidentalomas (AI) can be found in 3–10% of the general population. The vast majority of them (70%) represents nonfunctioning adrenal incidentalomas (NFAI). Although several comorbidities have been studied in patients with autonomous cortisol secretion (ACS) there are limited data for those with NFAI.
Aim
To study metabolic disorders frequency in patients with AI and especially NFAI.
Design
Retrospective study.
Methods
Seventy AI and 50 controls were recruited from the 1st Department of Internal Medicine in "Laiko" Hospital, Athens (Greece). NFAI were selected based on current guidelines. The control group was selected based on normal adrenal imaging exams (Computerized Tomography (CT)). Patients and controls were matched forage, sexand menopausestatus. Patients receiving any medication that could affectcortisol levels were excluded.
Results
Sixty patients (86%) presented NFAI and 10 patents ACS AI (14%). The 27% of the patients were diagnosed with bilateral AI and were more commonly classified as ACS compared to NFA ($P=0.005$). Adrenocorticotropic hormone (ACTH), urinary free cortisol levels (UFC) and cortisol levels after (1 mg-ODST) differed significantly between NFAI and ACS AI ($P<0.05$) as it was expected,in contrast with morning cortisol levels ($P=0.48$). AI size was higher in ACS compared to NFAI ($P=0.009$). The patients bearing NFAI and ACS AI had higher Body Mass Index (BMI) ($P=0.048$ and 0.02 respectively), higher fasting blood glucose ($P=0.009$ and 0.03) and Hb1Ac compared to controls ($P=0.04$ and $P=0.05$, respectively). The presence of NFAI was correlated with higher incidence of diabetes mellitus and hypertensioncompared to controls (33% vs 10%,and 37% vs11%, respectively). Serum cortisol levels in 1-mg ODST in NFAI group although normal (<1.8mg/dl) were positively correlated with Hb1Ac levels ($r=0.66$, $P=0.05$). No other metabolic disorders (i.e. dyslipidemia, osteoporosis) were correlated with the presence of AI.
Conclusions
The frequency of ACS among patients with AI is not negligible. Patients with NFAI exhibitmore commonly glucose metabolism disorders and obesity as compared to controls. Further investigations with larger sample are necessary to elucidate the aetiopathogenesis of metabolic disorders in this population.

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AEP105

Human centered design in co-creation of tool-kit for care of patients with adrenal insufficiency- an iterative quality improvement approach

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Background
The high prevalence of chronic disease urges for new ways of working with our patients as active members of the health care team to better design processes for ongoing supportive treatment. Our Division of Endocrinology & Metabolism at the University of Alberta prioritized the need to improve care for those living with adrenal insufficiency (AI). We have worked with AI patient partners to address learning needs and priorities of our patients, their caregivers, and health professionals.
Methods
We created a Divisional Quality Improvement (QI) team and trained members in theEvidence-based Practice for Improving Quality program (www.epiq.ca). For needs assessment and to better understand our local clinical context, we surveyed local endocrinologists on their current management approach for AI patients. In order to check provider assumptions and to ensure patient-centred care, we partnered with Human-Centred Design team and started AI patient engagement in a workshop series. We reviewed resources available in Canadian and international societies as a group, and used human-centred design methods to co-create new educational materials for improved AI shared decision making.
Results
15 endocrinologists filled the survey, revealing that existing endocrinologist practice and materials provided are variable and inconsistent. Five patient partners from the Canadian Addison Society joined our QI team. Using human centred design methods to review reported endocrine practice and explore needs and wants from the patient perspective. Our QI team prioritized development ofemergency room (ER) AI material and created an emergency card and emergency letter. We incorporated feedback from ER physicians and nurses to ensure end-user clinical acceptability.
Conclusion
The goal of these human-centred co-creations is to ensure that the AI resources support the educational needs of both patients living with chronic disease and clinicians during a clinical encounter. We believe materials developed from our collaborative approach incorporating cumulative experience and expertise from all stakeholders will result in improved care for our patients. Our QI team is working on a resource dissemination plan.

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AEP106

Study of effect of whitening creams on serum basal cortisol level in egyptian females

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Background
Topical corticosteroids (TCs) are widely used as depigmenting agents alone or in combination with other fairness creams. However, its use may cause secondary adrenocortical insufficiency.
Objective
The aim of the present study is to evaluate the relationship between practice of whitening creams (Topical Corticosteroids) and serum cortisol level in a sample of healthy females at Ain- shams University hospital.
Methods
We recruited 45 subjects practice whitening creams (TCs) for three months or more; matched with a healthy control group consists of 45 participants. Blood pressure BMI and early morning basal serum cortisol level (0800 h). Blood glucose, serum Na, and serum K were measured.
Results
Early morning serum cortisol level was statistically insignificant among subjects practice whitening creams with TCs vs healthy controls (*P* value 0.307). However, there were 7 out of 45 participants in the study group (15.6%) while none (0%)of the control group had low serum cortisol level (< 5 mg/dl) with highly statistically significant difference (*P* value <0.001). In comparison and data analysis between subjects of the study group regarding practice duration, used quantity, application frequency, and method of exposure, there was high statistically significant difference between subjects with normal cortisol level vs subjects with low cortisol level (*P* value <0.001). There were, no significant difference found regarding BMI, and arterial blood pressure between study group and controls.
Conclusion
Whitening creams abuse especially high potency TCs among Egyptian females may induce adrenal gland insufficiency.
Keywords: Serum cortisol level, Whitening creams, TCs.

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AEP107

A congenital adrenal hyperplasia patientpresented with myocardial infarction due to inadequate glucocorticoid therapy

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Congenital adrenal hyperplasia (CAH) refers to an autosomal recessive condition due to 21 hydroxylase (21OHD) deficiency, is characterized by impaired biosynthesis of glucocorticoid and mineralocorticoid. The consequent increase in the ACTH leads to bilateral adrenocortical hyperplasia and hyperandrogenism. Nonclassic CAH (NCCAH) manifests with a less severe clinic that presents later in life with the sympthoms of excessive androgen production. Clinical features include premature pubarche,acne, accelaration in bone age. Although this group often does not require continuous glucocorticoid (GC) replacement, most of the patients with NCCAH receive GCs for different range of durations. Overtreatment with GCs might lead to increases in cardiovascular risk factors. In contrast, insufficient GC therapy can lead to androgen excess,infertility,development of adrenal crest tumors. Our case, a thirty-seven year old male, presented with acute chest pain in the emergency room. Electrocardiographic evidence of ST-segment elevationin leads II, III and elevation in cardiac biomarkers correlated with acute inferior ST-elevated miyordial infarction. Coronary reperfusion was performedwith primary percutaneous coronary intervention to the infarct-related circumflex artery. In his medical history,he was diagnosed CAH at the age of ten but he gave up the glucocorticoid therapy four years ago. He was married with two children, both daughters (eight years old and five yerars old). His weight was 92 kg, height was 150 cm. Waist circumferencewas 112 cm. His body mass index was 40.8 kg/m² and his waist to height ratio was 0.74 kg/cm which were shown to be associated with an increase in insuline resistance. Theresults of the biochemical evaluations of the patient are presented in Table-1 which were more consistent with NCCAH according to moderate elevation in 17-OH progesterone levels. We planned genetic consultation. Low dose GC treatment and metformin was started along with antithrombotic therapy, regular endocrinologic follow-up was arranged. The increased cardiovascular risk in CAH patients mainly attributed to GC overtreatment in studies. In our case cardiovascular morbidity may be consistent with adrenal hypofunction and androgen excess, which may both lead to insulin resistance. It is essential to follow-up patients with CAH in terms of cardiovascular morbidity whether on GC treatment or not.

Table 1 The biochemical results of the patient.

Glucose	87 mg/dl
Triglyceride	411 mg/dl
Troponin T	1,34 ng/ml (0-0,014)
17-OH Progesterone	251,47 ng/ml
ACTH	112,7 pg/ml
Cortisol	3.42 µg/dl
Total Testosterone	1.19 ng/ml
DHEA-SO4	198 µg/dl

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AEP108

Paradoxical hypertension: The hidden risk of beta blockade

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Introduction
Betablockers are not a first-line antihypertensive therapy, although they have specific cardiological indications. The use of betablockers, especially the non-selective ones, may be associated with paradoxical hypertension, due to unopposed alpha-adrenergic peripheral vasoconstriction.

Methods
Review of the patient's Clinical Record and of the relevant literature.
Results
Clinical Case: A 66 year old woman was referred to our Outpatient Hypertension Clinic for evaluation of severe hypertension. She had no known allergies, did not smoke, her plasma glucose andlipid profile were normal, had underwent surgery of varicose veins in both legs. Her treatment included calcium plus vitamin D for osteopenia and alprazolam for anxiety (she was the main caretaker of her husband who had severe cognitive impairment). She did not take SSRI or MAO inhibitors. In the last two years she complained of uncontrolled hypertension in spite of multiple treatments, weight loss of about 3 kg, anxiety, tachycardia and tremor. She had consulted a private cardiologist, who ordered a transthoracic echocardiogram and a 24 hour ABPM. Both were reported as normal and she was prescribed propanolol. With this treatment she hads severe hypertensive episodes with SBP up to 250 mmHg with holocraneal headache, with pallor and nausea. Her blood pressure in our clinic was 136/81 mmHg, heart rate 77 bpm, her body mass index was normal and the physicalexamination was unremarkable. Lab tests (including plasma aldosterone and renin) were normal except for very high plasma normetanephrine (481.2 pg/ml, range 18–111) and slightly elevated metanephrine (64.9 pg/ml, range 12–60) The presuntive diagnosis is phaeochromocytoma/paraganglioma, as plasma normetanephrine was very high and the paradoxical hypertensive response to propanolol is characteristic. Abdominal CT and MIBG gammagraphy have been ordered and treatment with doxazosine has been instaured.
Conclusion
Betablockers should not be used in patients with uncontrolled hypertension in the absence of specific cardiological indication, until phaeochromocytoma/paraganglioma is ruled out. In the absence of alpha blockade, beta blockade may trigger severe hypertensive crisis.

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AEP109

Case study of family performing pheochromocytoma and paraganglioma (PPGL)

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Introduction
Phaeochromocytomas are mostly benign tumours with origin from chromaffin tissue of adrenal glands, whereas paragangliomas aretumours located along the sympathetic or/and the parasympathetic chain. Generally they are quite rare neoplasms with ability of producing, storing and secreting of catecholamines. Predominatingly they are sporadic, but in some cases they may develop in progress of particular genetic syndromes, such as multiple endocrine neoplasia type 2 (MEN II), neurofibromatosis type 1 (NF-1), Von Hippel-Lindau disease or Carney's Syndrome. Different defects in succinate dehydrogenase gene (SDH A, B, C, D) may be also detected. In this paper we would like to present a case of familiar PPGLs.
Case study
28-year-old woman with history of hypertension diagnosed during pregnancy, persistent after childbirth, was admitted to Chair and Department of Endocrinology of Medical University of Lublin (Poland) with suspicion of phaeochromocytoma. About 28 × 22mm lesion was visualised in right adrenal gland in routine ultrasonography imaging. In CT scannning performed in further stage of diagnostics, focal lesion of right adrenal gland about 37 × 31 mm in diameter and density about 37j.H. was detected, what aroused suspicion of pheochromocytoma. In diurinal urine collection elevated concentration of metanephrines, especially normethanephrine was detected. Patient was successfully operated after pharmacological preparation with doxazosin. Diagnosis of phaeochromocytoma was histopathologically confirmed. Simultaneously, 18-year-old man, the brother of above woman, was diagnosed with the presence of paraganglioma 56 × 26 × 28 mm in size of left side of his neck. Again elevated concentration of metanephrines, especially normethanephrine were detected in urine. Histopathological assessment after operation confirmed diagnosis of paraganglioma. At contiuous clinical and biochemical observation remain lesions in abdominal cavity of the patient.
Multiple neoplastic lesions originate from chromaffin tissue, present in siblings raise suspicion of familial PPGLs.
Conclusions
Pheochromocytomas and paragangliomas are extremely rare lesions derived from chromaffin-tissue with or without hormonal activity. In about 40 percent of cases, PPGLs are caused by a single driver germ line mutation. According to this data, patients with confirmed genetic mutations not only require more intensified follow-up, but also screening of family members is needed.

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AEP110

Pheochromocytoma with subclinical cushing's syndrome: A case report

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Introduction
Pheochromocytoma is a functional catecholamine producing tumor that originates from adrenal chromaffin cells and is an extremely rare cause of ectopic Cushing syndrome. We report clinical case of adrenal incidentaloma with the evidence of both pheochromocytoma and sub-clinical Cushing's syndrome.
Observation
A fifty-two year-old female patient was referred to our institution because of an incidentally discovered right adrenal mass. Although she had mild hypertension, she had no signs of excessive production of either catecholamines or adrenocortical steroids. Abdominal computed tomography revealed right adrenal solid mass with the diameter of 6 cm. The tumor was visualized as a heterogeneous mass with a central area of necrosis. Left adrenal gland was normal. The laboratory data demonstrated three times raised twenty four hours urinary fractionated metanephrines with non-suppressible serum cortisol after two-day low-dose dexamethasone suppression test. Her basal corticotrophin concentration was nineteen pg/ml. Pituitary magnetic resonance imaging (MRI) did not reveal any lesion. After pre-operative management with alpha blocker, she underwent laparoscopic right adrenalectomy. The pathologist concluded that the lesion was pheochromocytoma . The patient developed adrenal insufficiency after surgery and required glucocorticoid replacement therapy for eight months.
Discussion
Patients with ACTH-secreting pheochromocytoma are seen in five per cent of patients with the ectopic Cushing syndrome, and pose distinctive diagnostic and management challenges, but if diagnosed early and managed intensively they should be curable by surgery.
Conclusion
This case represents a very rare cause of ectopic Cushing syndrome caused by an ACTH producing pheochromocytoma. Extensive hormone profile evaluation should be carried out in all adult patients presenting with an adrenal mass independent of their clinical presentation.

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AEP111

A rare case of spontaneous adrenal haemorrhage from an adrenal haematoma

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Introduction
Severe haemorrhage from an adenoma is rare and potentially fatal. We report an unusual case of idiopathic unilateral severe adrenal haemorrhage from a non-functioning adrenal adenoma which was incidentally discovered 12 years earlier.
Case Presentation
A 59-year-old female was admitted to the hospital for a severe sudden onset of abdominal pain associated with vomiting. About 12 years ago, she was found incidentally to have a left adrenal adenoma of 2×1.7 cm of 8 Hounsfield Unit when she underwent CT abdomen investigating for anaemia. The adrenal hormonal work up of 24 h urine catecholamine and metanephrine, 24 h urine free cortisol and aldosterone-renin were unremarkable.

A repeat CT scan at 8 months later showed a stable adrenal lesion and she was discharged to her general practitioner. Her only other past medical history was diet-controlled hyperlipidaemia. She did not have hypertension, diabetes or obesity and did not take any medications. She did not have any symptoms to suggest pheochromocytoma. She denied any weight changes, fever or trauma. An urgent CT scan revealed a 9.7 × 7.2 cm acute haematoma in the left upper quadrant of the abdomen, likely related to a ruptured adrenal nodule. Her blood pressure inpatient was raised at 142–189/70–80 mmHg, likely due to the catecholamines release from adrenal haemorrhage. She was started on doxazosin to maintain normotension. 24 h urine catecholamines and metanephrines collected at 2nd day of admission were mildly raised which was appropriate for that level of stress (<1.5 times upper limit of normal). Her plasma free metanephrine (<0.20 nmol/l) and free normetanephrine (0.5 nmol/l) were normal. She did not have biochemical evidence of Cushing syndrome, hyperaldosteronism or hyperandrogenism. MRI adrenals performed on day 7 confirmed the enhancing left adrenal mass as the source of haemorrhage. Her abdominal pain resolved within the week and she was discharged well. Serial imaging of the adrenals using CT scan at 4 weeks and 5 months showed that the left adrenal size became progressively smaller, at 7 × 3.3 cm and 2.1 × 2 cm respectively. Her blood pressure control improved and she required only a low dose nifedipine 30 mg for control of hypertension at 5 months of follow up.

Conclusion

Idiopathic unprovoked adrenal haemorrhage from a non-functioning adrenal adenoma 12 years later can occur, suggesting that a longer follow up of adrenal adenoma should be considered before discharge.

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AEP112

A patient with seizures and adrenal failure as systemic manifestations of miliary tuberculosis: A case report

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Introduction

Extrapulmonary manifestations of tuberculosis can cause a diverse range of atypical presentations, depending on the system involved. Involvement of lymph nodes, pleura, central nervous system and bone are some of the organs that are well-described in the literature. This leads to a diverse range of presentations which can misguide diagnosis unless there is a high index of suspicion. Endocrinological manifestations are rare, but can occur uponhaematogenous dissemination of *Mycobacterium tuberculosis* in miliary tuberculosisto well-vascularised organs such as the adrenals, presenting with adrenal insufficiency or Addisonian crisis acutely.

Case description

We present the case of a 59-year-old man of South Asian origin, who presented in adrenal Addisonian crisis with a history of a significant, unintentional weight loss. He presented with classical signs of hyperpigmentation of the skin, hyponatraemia, hyperkalaemia and hypotension. A diagnosis of miliary tuberculosis was made based upon imaging, with suspected involvement of the adrenal glands. The patient improved with anti-tuberculosis chemotherapy and corticosteroid supplementation. The patient also later experienced tonic-clonic seizures and an altered personality, and magnetic resonance imaging later revealed several tuberculomas. The seizures were managed with levetiracetam, and corticosteroids were used to control tuberculoma development. Weaning of corticosteroids was necessary to conduct a short synacthen test. However, this repeatedly led to the patient being admitted on further occasions, presenting with similar signs of adrenal insufficiency. Eventually when a short synacthen test was conducted, it was able to demonstrate a lack of a cortisol response, which combined with high levels of adrenocorticotrophic hormone and bilaterally enlarged adrenals, suggested the patient was experiencing primary adrenal insufficiency secondary to extrapulmonary tuberculosis of the adrenals.

Discussion

The systemic manifestations of tuberculosis are complex, with little literature available regarding the involvement of adrenal glands. This case report describes the progression of possibly long-standing miliary tuberculosis to cerebral tuberculoma and adrenal tuberculosis, likely through lymphohaematogenous spread. Immunosuppressive therapies and the HIV/AIDS pandemic is likely to increase the incidence of unusually presenting extrapulmonary manifestations of tuberculosis. Therefore, it is important to acknowledge adrenal insufficiency and seizures as potential presentations of tuberculosis, particularly in the context of disseminated miliary tuberculosis.

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AEP113

Misdiagnosis of phaeochromocytoma with multiple cerebral infarcts and complex arrhythmias, failure "to think of it"

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The classic episodic triad of headache, sweating and palpitations facilitates the diagnosis of phaeochromocytoma. The absence of these symptoms can lead to misdiagnosis in patients with uncommon symptoms attributable to phaeochromocytoma. We present such a case.

Case report

A 64 year old man was referred to endocrinology having been coincidentally found to have a right adrenal mass with features of a phaeochromocytoma. He was asymptomatic and engaged in regular formal exercise. Hypertension diagnosed seven years earlier was treated with bisoprolol, amlodipine and losartan. Five years earlier multiple cerebral infarcts were found on presentation with sequential neurological deficits. Our biochemical and imaging investigations confirmed a diagnosis of solitary phaeochromocytoma.24 hour blood pressure monitoring revealed extreme lability exceeding the normal limits of cerebral autoregulation of blood flow.24 hour electrocardiography revealed episodes of asymptomatic trigeminy and ventricular tachycardia. Alpha blockade with doxazosin improvedblood pressure lability with resolution of arrhythmias prior to laparoscopic adrenalectomy. At the time of diagnosis of multiple cerebral infarcts the stroke team initially found mild weakness and reduced sensation in the right arm. A diagnosis of cervical myelopathy was supported by finding degenerative changes on x-ray. One week later he developed visual disturbance and was found to have a left homonymous hemianopia. CT brain confirmed infarction in areas perfused by the middle cerebral artery. MRA was normal but MRI confirmed right parietal, occipital and cerebellar infarcts. These findings led to extensive investigations with involvement of cardiologists, haematologists and neurologists. Such investigations excluded vasculitis, thrombophilia, diabetes, HIV and sarcoid.4-D cerebral CT angiography, transthoracic and transoesophageal echocardiography were normal. Seven day electrocardiography detected asymptomatic episodes of atrial fibrillation and complex ventricular tachycardia. Repeat MRI confirmed a new large pontine infarct. Throughout the investigations blood pressure ranged from 108/61 mmHg to 130/80 mmHg. He was discharged to primary care following anti-coagulation with warfarin with a putative diagnosis of multiple cerebral infarcts secondary to embolic events.

Discussion

This case confirms the presentation vagaries of phaeochromocytoma, it remains "the great mimic".Colleagues who managed him previously confirmed a failure to "think of it", particularly in view of the apparently normal blood pressure levels. It behoves endocrinologists to highlight the protean manifestations of phaeochromocytoma, particularly in patients with unexplained cerebrovascular events and arrhythmias.

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AEP114

Can you diagnose drug-induced bilateral adrenitis before clinical and analytical manifestations are present?

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Introduction

The introduction of immunotherapy with checkpoint inhibitors for oncologic diseases has improved the survival and quality of life of our patients; however, these therapies are frequently associated with autoimmune endocrine disease.

Methods
Revision of the patient's clinical record and the related literature.
Results
Clinical Case : An 88-year old woman was referred to our Endocrinology Clinic because of a PET image suggestive of bilateral adrenitis. Her history included essential hypertension and dyslipidaemia, treated only with enalapril 20 mg and atorvastatin 20 mg daily. She had been diagnosed in 2015 of melanoma with primary lesion in the right foot and extensive systemic metastases. She was treated with stereotactic body radiation therapy (I-SRBT) and conventional chemotherapy, plus eight cycles of pembrolizumab. Afterwards her melanoma was in complete remission, and the patient was asymptomatic except for asthenia and right malleolar oedema. A control PET was performed, showing bilaterally enlarged non-nodular adrenals (SUVmax 4.1 right adrenal, 5.8 left), suggesting bilateral adrenitis elicited by immunotherapy. Lab tests showed normal adrenal axis function, with glomerular filtration rate (CKD-EPI) 52 ml/min 1.73 m², Na^+ 142 mEq/l, K^+ 5.5 mEq/l, cholesterol 211 mg/dl, triglycerides 113 mg/dl, ACTH 12.6 pg/ml, cortisol basal 17.3 µg/dl. At this point she was referred to our Endocrinology Clinic. The presumptive diagnosis was bilateral adrenitis attributable to immunotherapy, without clear clinical or analytical manifestations. We ordered new lab tests. 2 months later the patient had very low fasting plasma cortisol (2.90 mg/ml) and aldosterone (3.7 ng/dl) with normal plasma ions, but her asthenia had improved, and she remained without treatment. A new lab control 2 months afterwards showed full recovery of her adrenal function (aldosterone 31.5 ng/dL, test ACTH → cortisol: 19.6, 25,10 and 24.7 mg/dl at 0', 30' and 60', while a new PET scan showed lower adrenal activity (SUVmax 2.74 left, 2.24 right).
Conclusions
The new checkpoint inhibitors such as pembrolizumab unleash an autoimmune aggression against the neoplastic cells, but collateral damage is frequent and autoimmune disease affecting the thyroid, the adrenal glands, the hypophysis and/or the endocrine pancreas is a common occurrence. The peculiarity in our patient was that there was evidence of drug-induced adrenitis before the biochemical and clinical manifestations were apparent.

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AEP115

Severe hypoaldosteronism after unilateral adrenalectomy for aldosteronoma: Case report

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Introduction
Primary aldosteronism is characterized by hypertension and accounts for about 10% of hypertensive patients. Post-operative hypoaldosteronism is well documented in cases within the past 3 years of unilateral adrenalectomy for aldosterone-producing adenomas.
Case report
We present the case of a 46-year-old patient with a 10-year history of hypertension and hypokalaemia (1.9 mmol/l) with normal renal function. Serum aldosterone was high with low renin activity leading to high aldosterone to renin ratio. Serum creatinine was 67 umol/l. CT abdomen showed 1.5 cm hypodense left adrenal mass. Post unilateral adrenalectomy he had reduction in the blood pressure, became eukalemic. After 8 weeks of adrenalectomy patient developed hyperkalemia (6.4 mmol/l) and increased serum creatinine (161 umol/l). Nephrology was recommended furosemide 80 mg daily. After furosemide, his kalium dropped to 5.8 mmol/l, creatinine to 149 umol/l. After 9 weeks, he presented to our department with muscle cramps, weakness, intermittent cardiac arrhythmia, and hyperkalemia (6.2 mmol/l), hypocalcaemia (1.82 mmol/l), hyperphosphatemia (1.9 mmol/l), the serum creatinine (158 umol/l) and parathyroid hormone (135 pg/ml) were high, aldosterone (16.3 pg/ml) and 25(OH)D (11.4 ng/ml) were low. After fluid resuscitation he was started on fludrocortisone 0.1 mg, calcium carbonate 1500 mg daily, and cholecalciferol 50.000IU weekly. His furosemide was reduced to 20 mg in a day. Two weeks later his creatinine was 126 umol/l,kalium 5.3 mmol/l, calcium 2.2 mmol/l, phosphat 1.6 mmol/l. His blood pressure was 138/85;therefore, he was switched to furosemide 20 mg once daily. Two months later his serum creatinine was 109 umol/l, kalium 4.8 mmol/l, calcium 2.31 mmol/l, phosphat 1.35 mmol/l, parathyroid hormone 83 pg/ml, 25(OH)D 29.1 ng/ml and so a dose reduction in fludrocortisone was attempted but at 0.05 mg per day, her kalium promptly rose to 5.2 mmol/l with creatinine 118 umol/l. The furosemide was stopped and fludrocortisone dose increased again with similar normalization of kalium and creatinine. Two months later off of the fludrocortisone 0.1 mg, his blood pressures were 145/85 and a dose reduction in fludrocortisone was attempted again. During the last 5 weeks on fludrocortisone 0.05 mg daily andcholecalciferol 10.000 IU weekly, his blood pressures (120–130/70-75), kalium (4.9–5.0 mmol/l),-calcium (2.34 mmol/l),parathyroid hormone (54 pg/ml) have been normal with stable renal function (creatinine 100–103 umol/l).
Conclusion
Screening of developing post-operative hypoaldosteronism with hyperkalemia should be actively considered in high-risk patients.

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AEP116

Adjuvant mitotane therapy: Predictive factors of response in adrenocortical carcinoma

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Introduction
Adrenocortical carcinoma (ACC) is a rare and aggressive tumor, with a poor prognosis and median survival of 3–4 years. Complete surgical resection is the only possibility of cure. The rate of post-surgical recurrence is high, so adjuvant treatment with mitotane plays a key role.
Objectives
To evaluate predictive factors of response to adjuvant treatment with mitotane in monotherapy in patients that underwent surgical resection of ACC.
Material and methods
Retrospective study of medical records of ACC patients from March/1991 to May/2019. Analysis of clinical, biochemical, imaging and anatomopathological variables (Ki-67 and Weiss score) and their predictive role in response to adjuvant treatment with mitotane. Some patients did not have a description of all Weiss criteria. Results with $P<0.05$ were considered statistically significant.
Results
Of the 34 patients, 22 were excluded (4 were not operated and 18 received mitotane in combination with chemotherapy and/or metyrapone and/or radiotherapy). Twelve patients were included. The average age at diagnosis was 50.5±14.6 years, with 83.3% being female. At presentation 50.0% of patients had symptoms of hormonal hypersecretion, 25.0% had constitutional symptoms and 25.0% were diagnosed as incidentaloma. The laparotomy was the preferred surgical approach ($n=7$; 58.3%). Complete tumor resection occurred in 8 patients (72.7%). The initial median dose of mitotane was 1.5 g/day (IQR:1.5), with an average maximum dose of 4.4±2.6 g/day (minimum: 2.0; maximum: 8.0). The average time interval to reach the maximum daily dose of mitotane was 4.7±3.9 months, with an average maximum mitotanemia of 14.5±7.7 mg/l. 83.3% of patients reported treatment-limiting adverse effects, with a predominance of gastrointestinal effects. The median duration of therapy was 12 months (IQR:38.0; minimum: 1.0/maximum: 68.0). 25.0% had a complete response, without evidence of disease until the present time. The median survival was 18 months (IQR:38.3; minimum: 4.0/maximum: 113.0). In the univariate analysis, only the presence of atypical mitoseswas significant. The disease persisted in all cases with it vs 33% in the absence of atypia ($P=0.023$). Gender, age, other imaging and anatomopathological characteristics, hormonal statusin the preoperative period, initial dose of mitotane, level of mitotanemia, and time to maximum dose or duration of therapy, were not predictive of the response.
Conclusions
In this study, the presence of atypical mitoses was the only significant survival predictor. Mitotanemia at the lower limit of the therapeutic window or even lower and the small sample size conditioned by the rarity of the pathology may have contributed to the results.

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AEP117

Diagnosis, treatment and survival of adrenocortical carcinoma: 28 years of experience

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Introduction
Adrenocortical carcinoma is a rare endocrine disease characterized by an aggressive behaviour with a poor prognosis. Clinical experience, even with a little number of patients, has enhanced knowledge about this malignancy, in most cases challenging.
Objective
Characterization of patients with adrenocortical carcinoma followed at the endocrine department of a hospital centre, between 1991 and 2019.
Methods
Retrospective cohort study, based on clinical records of patients with histopathologic confirmed result of adrenocortical carcinoma. Statistical analyses with SPSS v.25.
Results and conclusion
We obtained 34 patients: 79.4% female, mean age at the diagnosis 50.03±13.02 years. Clinical presentation: 50% (n=17) - symptoms of adrenal hormone excess, 32% (n=11) - low back/abdominal pain or weight loss, 18% (n=6) - adrenal incidentalomas. Computerized tomography scan (CT) data: mean tumour size - 10.5±4.2 cm, necrosis imaging- 80%, CT density >10UH - 100%, additional invaded organs – 35.3% (mainly kidney and inferior cava vein), metastases at the diagnosis – 26.5%. Laboratory analysis: functional tumours (71%, n=24); hypercortisolism – n=11; hypercortisolism and androgen excess – n=9; androgen excess – n=3, hypercortisolism, androgen and mineralocorticoid excess – n=1. Surgery treatment was performed on 88.2% (n=30) of patients. Surgical approach: open surgery – 67% (n=20), laparoscopic adrenalectomy – 32% (n=10). Resection: R0 – 72.4%, R1 – 24.1%, R2 – 4.4%. ENSAT stage: 66.7% (n=20) in the stage II, 20% (n=6) in stage III, 13.3% (n=4) in stage IV. Histopathologic analysis: median of weight tumour – 260.5 g(680 g), between 71-2600 g; mean Weiss-score – 5.36±1,55; mitotic rate (>5 per 50 high-power fields) – 73.3%, abnormal mitoses – 68.4%, cytoplasm with clear cells comprising 25% or less of the tumour – 84.6%, necrosis – 91.7%, capsular invasion – 62.5%, mean Ki-67 index –26.2±22.8. Medical adjuvant therapy was performed on 70.6% (n=4) patients: mitotane monotherapy (n=12), mitotane and chemotherapy (n=5), mitotane and metyrapone (n=5), mitotane, chemotherapy and metyrapone (n=2). Radiotherapy was performed only on one patient. Relative to mitotane therapy: median initial dose – 1.5 g/day (1.5), median of maximum dose –5.4 g/day (3.0); mean of mitotane plasma level – 14.8±7.9 mg/l. Therapeutic mitotane plasma level was reached at 60% of patients. The mean overall survival was 52.2±79.1 months and was higher in youngers patients (r=-0.09; P=0.596). Actually, 12 patients are alive, 11 of them with complete remission. Despite the poor prognosis of this malignancy, the high survival rate and the high number of patients on complete remission found in this series (32.4%) is highlighted.

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AEP118

CT signs and parameters of vascularization of pulmonary neuroendocrine tumours and their relationship with the development of ACTH ectopic syndrome

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Purpose
To analyze CT signs and parameters of vascularization of pulmonary neuroendocrine tumours (PNT) and their relationship with the development of ACTH ectopic syndrome.
Materials and methods
23 patients with PNT were evaluated with contrast-enhanced MDCT. Arterial and venous phases were obtained at 10 and 35 seconds after the attenuation of 200 HU at the descending aorta, a delayed phase was at 6–8 min after the start of injection of contrast media. The final diagnosis was established after histological and immunohistochemical analyses. "Typical carcinoid" (16 patients), "atypical carcinoid" (7) were revealed. ACTH ectopic syndrome was in 9 (56,3%) patients with TC and in 2 (28,6%) with AC. The following qualitative signs were analyzed at CT scans: localization of PNT, shape (round, oval, irregular), contours (smooth, tuberous, spiculate), its relationship with bronchus/vessel (stenosis, invasion, intimate adherence, presence of a feeding vessel), structure (necrosis and calcifications (localization and size). The surrounding parenchyma (ground glass opacity, lymphangitic carcinomatosis, areas of fibrosis, atelectasis, infiltrative changes), pleural thickening, bronchiectasis, pleural effusion were analyzed. The following quantitative signs were analyzed: the size of the PNT and the largest regional lymph node, patterns of the time-density curves (TDC). The precontrast density, peak height in density (PH: the maximum value of the TDC) and S/A ratio (the ratio of the PH of lesion to aorta) were recorded. Precontrast density and enhancement patterns of lesions were recorded. Perfusion of the lesions was calculated.
Results
The moderate relationship between ACTH ectopic syndrome and following CT features was revealed: perfusion (r=0.567, P=0.007), S/A ratio (r=0.504, P=0.02) and size of lesion (0.540, P=0.008). A very good quality of predictive model for the perfusion of the lesion and its size was determined (AUC 0.827, P=0.011, AUC 0.811, P=0.012). Perfusion rate 0.86 ml/min per ml and tumor size 12.5 mm ware the cut-off value (sensitivity 72.7%, specificity 80%, sensitivity 100%, specificity 54.5%). A good quality of predictive model for S/A ratio (AUC 0.791, P=0.024) was determined. S/A ratio 36.8% was the cut-off value (sensitivity 54.5%, specificity 100%).
Conclusions
The following findings: small size of the lesion (less than 12.5 mm) and low parameters of perfusion and S/A ratio allow us to suspect a hormonal activity of carcinoid tumor and, consequently, a more malignant nature of tumour, which should be taken into account in treatment strategy.

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AEP119

A retrospective review of radiological and endocrine characteristics of adrenal incidentalomas,in an Irish regional hospital

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Objective
To identify the radiological characteristics of adrenal abnormalities as reported on CT abdomen;To identify functional characteristics of adrenal incidentalomas; To identify 12 month outcomes of adrenal incidentalomas
1500 consecutive unselected computerised Tomograms(CT abdomen) done for non-adrenal indication, reviewed for adrenal abnormalities to identify, the incidence size, radiological density, those with abnormalities underwent endocrine work-up and re-imaging as advised in the European endocrine society guidelines.1500 scan were reviewed, Total abnormalities identified in the adrenal in 60 scans. Adrenal Adenomas wereidentified in 55, of which 1 was >4 cm, 1 were 3-4 cms in size, 5 in the 2-3 cm range, 18 in the 1-2 cm range and 30 in the sub centimetre range. 5 non-specific abnormalities were also identified.75% of all lesions were non-functioning adenomas. 12% had non-suppressed cortisol on overnight 1 mg Dexamethasone suppression. 2% patients had features of aldosterone over secretion, and 1 percent had phaeochrochromocytoma. Repeat scanning at 12 months was done on 25 of these adenomas that were ≥1 cm and no significant interval change in their size or appearance was identified in any of the adrenal incidentalomas on re-imaging. Our study is the first study of adrenal incidentalomas in the Irish midlands and broadly confirms the accepted European prevalence of adrenal incidentalomas of 0.04% for CT abdomen. Furthermore, it demonstrates that functionally 1 out of every 5 of the adrenal incidentaloma may have features of adrenal autonomous secretion. And cortisol oversecretion was the commonest endocrine abnormality detected in this cohort.

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AEP120

A 17-year-old Takotsubo cardiomyopathy patient exhibiting SDHB (+) PPGL and hypersecretion of insulin at 15 minutes after glucose loading

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A 17-year-old woman was hospitalized emergently after suffering sudden palpitations and losing consciousness. On admittance she was in a state of shock, with a pulse rate of 140/min and systolic blood pressure of 70 mmHg. Echocardiography revealed a diffuse wall hypokinesis with decreased left ventricular ejection fraction. Acute heart failure was diagnosed. Coronary angiography, LV imaging, and myocardial biopsy suggested fulminant Takotsubo cardiomyopathy due to catecholamine hypersecretion, with urine normetanephrine 1350 ng/mg/Cr and urine noradrenaline 728 µg/day (noradrenaline dominant). Other endocrine hormones were in the normal ranges. Paraganglioma (PPGL) was suggested by an abdominal-CT showing a well-defined 33 × 22 mm tumor in the right retroperitoneum and by MRI showing hypointensity on T1-weighted image and a high intensity on T2-weighted image. Scintigraphic and PET-CT evidence of accumulated MIBG confirmed solitary PPGL in the right retroperitoneum. The tumor was surgically removed, and clear evidence of the SDHB mutation was confirmed. The 75 g OGTT test was performed before and after the surgery. Blood glucose (mg/dl) was normal high before resection, and improved after resection. The patient's IRI value, an all rose sharply at 15 minutes after the preoperative glucose loading. Improvements over the initial secretion expressed by the insulinogenic index (I.I.), the secretion expressed by HOMR-β (significant), and the resistance expressed by the HOMA-IR and Matsuda index were observed.[Discussion] This case has been presented as acute catecholamine cardiomyopathy, Takotsubo cardiomyopathy due to PPGL. Among the various genetic mutations that influence PPGL, those in genes encoding subunits of succinate dehydrogenase are the most relevant. As a mechanism of impaired glucose tolerance in catecholamine-producing tumors, noradrenaline dominance has been reported to lower insulin sensitivity and promote hepatic gluconeogenesis. In our case, hypersecretion of insulin was observed 15 minutes after the glucose loading before resection of the catecholamine-producing tumor, and improvements in the hypersecretion of insulin and insulin resistance were obtained after the tumor was excised. The catecholamine-producing tumor did not appear to impair early insulin secretion in our case. In this case exhibiting insulin hypersecretion at 15 minutes after glucose loading before tumor resection, the insulin secretion seemed to increase in a blood glucose-dependent manner.

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AEP121

Melatonin inhibits vascular smooth muscle cell proliferation and apoptosis through upregulation of Sestrin2

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Melatonin inhibits vascular smooth muscle cell proliferation and apoptosis through upregulation of Sestrin2

Excessive vascular smooth muscle cell (VSMC) proliferation contributes to the development of atherosclerosis and restenosis. On the other hand, apoptosis of VSMCs accelerates plaque rupture in the atherosclerotic vessels. Therefore, a strategy that regulates both VSMC proliferation and apoptosis is essential for the development of new pharmacological tools for the treatment of atherosclerosis. Despite mounting evidence supporting the benefits of melatonin in diverse metabolic diseases, the role of melatonin in VSMC growth remains largely unknown. In this study, we found that melatonin inhibited both proliferation and apoptosis of primary cultured rat VSMCs. Melatonin induced mitochondrial energetic stress in VSMCs and subsequent induction of Sestrin2 via C/EBPβ. Melatonin-induced Sestrin2 suppressed mTORC1 activity in VSMCs, contributing to suppression of VSMC proliferation. Moreover, melatonin-induced upregulation of Sestrin2 blocked apoptosis by preventing excessive ROS generation. Our results show that melatonin controls both VSMC proliferation and apoptosis via Sestrin2-mediated inhibition of mTORC1 and ROS scavenging. Therefore, melatonin should be considered as a lead compound for therapies aimed at preventing vessel lumen constriction during the course of atherosclerosis and restenosis.

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Bone and Calcium

AEP122

Phase 3b open-label study of burosumab in adults with X-linked hypophosphatemia (XLH): Baseline and Week 12 results

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Introduction

Burosumab, a fully human monoclonal antibody to fibroblast growth factor 23 (FGF23), is the only approved treatment for XLH, a rare genetic disorder characterized by renal phosphate wasting and substantial cumulative musculoskeletal morbidity. BUR02 (NCT03920072) is a European phase 3b open-label study monitoring the long-term safety and efficacy of burosumab in adults with XLH from sites who participated in the CL303/CL304 studies (NCT02526160/02537431).

Objective

To describe the patients in the open label follow-up and the first 12 weeks data from BUR02.

Methods

Forty-eight adults with XLH who participated in CL303/CL304 studies from EU sites were invited to take part in BUR02 and continue to receive burosumab every 4 weeks. Thirty-seven patients are expected to be recruited in total. Patients attended the clinic at baseline and week 12 for measurement of serum phosphate (primary endpoint) and patient-relevant secondary endpoints, and collection of safety data.

Results

Baseline and Week 12 data from BUR02 are available for 27 subjects (median age 46 years [range 22–63 years]; 66.7% female).At BUR02 baseline their median height was 150 cm, height z-score -2.2, BMI 25.6 kg/m^2 and 96.3% had a pathogenic *PHEX* gene variant, 52% were taking pain medication, 81% had joint pain and 67% had received prior orthopaedic surgery. Median serum phosphate was 0.7 mmol/l (2.3 mg/dl) at baseline and 0.8 mmol/l (2.4 mg/dl) at Week 12. Median Brief Pain Inventory (BPI) scores at baseline and Week 12 were 5.8 and 6.0 for worst pain, and 3.0 and 3.6 for pain interference. Median Brief Fatigue Inventory (BFI) scores were 5.8 and 6.0 for worst fatigue, and 2.7 at both timepoints for fatigue interference. Median Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were 45.6 and 36.8 for physical functioning, 50.0 at both timepoints for stiffness, 45.0 at both timepoints for pain, and 46.9 and 41.7 for total score respectively. Median Short-form-36 v2 scores at Week 12 were 39.0 for the physical component score (PCS) and 49.3 for the mental component score (MCS).Median 6-minute walk test (6MWT) distance was 412 m at baseline (58.8% predicted) and 423 m (62.9%) at Week 12. There were no serious adverse events in the first 12 weeks of BUR02.

Conclusion

Early analysis of the first 12 weeks of BUR02 data demonstrates that continuation of burosumab from the CL303/304 studies into BUR02 sustains the correction of serum phosphate levels and maintains clinical benefits in patients.

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AEP123

Usefulness of parathormone (PTH) needle washout measurement vs MIBI scintiscan in localization of parathyroid adenoma- a single-center based preliminary study

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Introduction
An accurate identification of affected parathyroid is crucial for implementation of mini-invasive surgery techniques and therefore reduction of complication rate. A few centers postulate measuring washout parathormone (PTH) concentrationin suspected lesions, despite lack of established cut-off point for concentration values and validated measurement methods. Thisprospective study aimed to compare washout PTH assessment vs MIBI scintiscan in terms of efficacy in localization of parathyroid adenoma (PTA) in patients with hyperparathyroidism (HPT).
Material and methods
55 consecutive HPT patients (including seven males) aged 59±12 years were included. Median serum PTH was 133 mg/dl (range 83–148; normal 15–57), total calcium 11.2±1 mg/dl, ionized calcium 6.1±0.7 mg/dl, phosphates 2.8±0.6 mg/dl. Median maximum diameter of the lesion was 8 mm (range 3–40) on ultrasound. The most common location was left lower thyroid pole ($n=18$). The needle washout was performed in 1ml 0.9% NaCl. PTH concentration was measured by electro-chemiluminescence third-generation immunoassay Elecsys PTH 1–84 using cobas e 801 analyzer. Thyroid and parathyroid ultrasound was performed by an AIXPLORER system (Supersonic Imagine, Aix en-Provence, France).
Results
Median PTH washout concentration was 1493 pg/ml (range 17.2–5000). Positive PTH washout result (≥3 times above serum PTH value), was obtained in 76% of subjects. In lesions with ultrasound picture typical of PTA ($n=45$), PTH washout was positive in 82%. PTH values were significantly higher in typical than atypical lesions ($P=0.026$). Among patients with negative PTH washout ($n=13$), 85% had nodular goiter and/or autoimmune thyroid disease (AITD). MIBI performed in 53 patients, provided localization of PTA in 68%. In subgroup with negative MIBI, 13 subjects (76%) had positive PTH washout (location confirmed surgically in 3, 8 awaiting surgery, 2 followed-up).According to clinician, more useful in terms of PTA location was PTH washout alone in 30% of cases, especially in lesions <1 cm (33% vs 25% for MIBI), MIBI alone in 21% of cases, for the rest both methods were equivalent.
Conclusions
PTH washout assessment using the same method as for serum PTH measurement isa reliable method of PTA localization,particularly useful for lesions <1cm, with typical ultrasound features of PTA, without concomitant nodular goiter or AITD and negative MIBI results, although is not yet widely validated by lab technicians. Despite slight preponderance of PTH washout above MIBI alone, combination of both methods seems to be the most valuable. The study will be continued to reach relevant endpoint after surgery.

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AEP124

«Angio Scan-01» for extraskeletal calcification assessment in patients with mineral and bone disorders in chronic kidney disease

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Background
Mineral and bone disorders in chronic kidney disease (CKD-MBD) is a systemic disorder of mineral metabolism due to CKD, which is manifestedby abnormalities of calcium, phosphorus, parathormone (PTH) and vitamin D; renal osteodystrophy; extraskeletal calcification. In patients with CKD, vascular calcification occurs 10–20 years earlier than in the general population, and is highly prevalent (40–92%) in the hemodialysis population. «AngioScan-01» is a professional diagnostic device for assessment of arterial function state and seems promising as a screening method for calcification detection in CKD patients.
Aim
To evaluate the diagnostic value of «AngioScan-01» device for theextraskeletal calcificationdetection in CKD patients compared totraditional noninvasiveimaging tools.
Methods
22 patients with secondary hyperparathyroidism (SHPT) were includedin the study, and 19 of them received hemodialysis. Calcification was estimated using echocardiography, doppler sonography of peripheral arteries, plain lateral lumbar X-rays, AngioScan-01 device. Laboratory tests included serum phosphorus, calcium, albumin, PTH, triglycerides, cholesterol (total, high-density lipoprotein, and low-density lipoprotein).Data analysis was performed with the Statistica 13 package (StatSoft, USA) and SPSS (IBM, USA).Quantitative data were assessed for normal distribution using the Shapiro – Wilk's W-test. Multiple and logistic regression were used to detect calcification predictors. A prognostically significant model was considered at $P<0.05$.
Results
Calcification was found in all examined patients: calcification of arterial and mitral heart valves in 54.5% (12/22 in both cases), in total femoral artery in 45.4% (10/22), and in common carotid artery in 36.4% (8/22), the thoracic aorta in 45.4% of cases (10/22), the abdominal part in 54.5% (12/22). Calcification according to «AngioScan-01» device was detected in 68.2% (15/22). The sensitivity and specificity of «AngioScan-01»compared to echocardiography was defined as 68% and 33%, with Doppler scanning as 80% and 57%, with X-rays as 86% and 71%respectively. Thelogistic regression analysis confirmed a statistically significant relationship of calcification with serum phosphorus level and calcium-phosphorus products ($P<0.05$, average for phosphorus 1.87±0.49 mmol/l,for calcium-phosphorus products 4.53±1.44 mmol/l), but did not indicate this for calcium, parathyroid hormone levels, the severity of anemia and dyslipidemia, which may be associated with a small number of patients.
Conclusion
The «AngioScan-01» method showed diagnostic value in the vascular calcification detection in patients with SHPTin CKD and could be introduced as a simple screening method into clinical practice.
Keywords: secondary hyperparathyroidism, chronic kidney disease, vascular calcification.

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AEP125

Impaired bone health at cancer diagnosis in paediatric patients

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Objectives
To evaluate the skeletal profile of paediatric patients with cancer at diagnosis.
Methods
Children diagnosed with cancer in our Oncology Centre were recruited during a two-year period and underwent metabolic bone profile and dual-energy X-ray absorptiometry (DXA) at the time of diagnosis.
Results
88 children were evaluated (51 boys, 53 prepubertal), aged 7.6±4.6 years. Of those, 50 were diagnosed with haematological malignancies and 37 with solid tumours. 21 out 69 patients had bone pain, (15 had a limp pain) and one sustained a femoral fracture. 43.2% (38/88) of the patients were vitamin D insufficient (25-OH-D: 12–20 ng/ml) and 5.7% (5/88) were deficient (25-OH-D <12 ng/ml). Hyperparathyroidism was present in 11.4% and hypercalciuria in 30% of all patients. One patient with hepatoblastoma had rickets. Bone turnover was also affected, particularly bone formation, because the patients had lower levels of osteocalcin (OC, $P<0.001$) and procollagen type I propeptide (PICP, $P=0.001$), compared to controls. Subgroup analysis revealed lower bone formation markers in the haematological subgroup i.e. OC and PICP ($P=0.001$ for both markers), whereas the solid tumour subgroup had higher bone resorption markers: tartrate-resistant acid phosphatase and urine deoxypyridinoline/urine creatinine ($P=0.002$ for

both markers).
DXA scan was performed in 47 patients; 21,2% (10/47) of them had low-normal bone mineral density (BMD) of the lumbar spine (LS BMD Z-score between –1 and –2) and only one patient had low BMD Z-score <–2 at the same site. Two patients had low/normal BMD of total body less head scans.
Conclusion
Skeletal health is already affected at the time of diagnosis in paediatric cancer patients. Low vitamin D levels are common. Bone turnover is disturbed and follows different patterns, depending on the type of cancer. These observations support bone health surveillance and early intervention at the time of diagnosis.

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AEP126

Abstract withdrawn

AEP127

Familial hypocalciuric hypercalcemia in a young man: Grey zones of the differential diagnosis in 10-year clinical follow up

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Herein, we report currently a 39-year old male with a 13-year history of asymptomatic hypercalcemia (mean 2.88 mmol/l; reference range 2.15–2.55 mmol/l) and mildly elevated parathyroid hormone (mean 68.7 ng/l; reference range 15–65 ng/l). Initially, in years 2007–2010 his laboratory picture was compatible with the diagnosis of Familial hypocalciuric hypercalcemia (FHH) with calcium-to-creatinine clearance ratio (Ca/Cr) between 0.008–0.009.Genetic testing was not available at that time. The differential diagnosis from primary hyperparathyroidism (PHPT) was complicated by the fact that there was no other family member with documented hypercalcemia. Between years 2014–2016 his follow up was interrupted. When he came in 2017, his Ca/Cr has almost doubled (0.014–0.019), whereas serum calcium has remained at a constant and moderately elevated level. To rule out a parathyroid adenoma, the patient underwent Tc-sestamibi scintigraphy (negative) and PET-CT with fluorocholine revealing an active focus bellow the left thyroid lobe. The neck ultrasound did not find any lesion corresponding to an enlarged left lower parathyroid gland. The Calcium-sensing receptor gene sequencing was finally carried out and identified a heterozygous missense mutation in exon 6 (c.1670G>A, p.Gly557Glu). This mutation has been previously reported in a Japanese family. Unlike our proband, all family members with G557E mutation had Ca/Cr lower than 0.01 in line with FHH. Although bone densitometry showed normal bone mineral density (BMD) in our male patient, there was a significant decrease in BMD between years 2009–2017 (22% at the femoral neck, 14% at total hip and 4.5% at lumbar spine). The documented bone loss corresponded to annual BMD % change of 2.75 at the femoral neck, 1.75 at total hip and 0.6 at lumbar spine. The patient did not have any other obvious reasons for bone resorption (no medication, normal body mass index, no endocrinopathy, vitamin D sufficiency) and it remains to be elucidated.
The biochemical profile of FHH and PHPT may overlap. The present FHH patient illustrates that the differential diagnosis can be difficult in an index case with (false) positive parathyroid imaging. Moreover, his Ca/Cr fluctuated in a large range (0.007–0.0198).Calcium intake, vitamin D status and bone resorption might have contributed to the patient Ca/Cr variations in 10-year clinical follow up.
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AEP128

Ultrasound-guided laser thermal ablation for parathyroid adenomas - preliminary report

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Background
The curative therapy of primary hyperparathyroidism (pHPT) is surgery. Data about ultrasound-guided laser ablation (LA) of parathyroid tumor are limited, however it could be a solution for patients with high surgery or anesthetic risk. We report our experience on LA of parathyroid tumors in 11 patients with pHPT with high surgery or anesthetic risk.
Methods
LA was performed under ultrasound guidance with an output power of 3W. Total energy and time of ablation was set individually, to make the ablation zone (monitored with real-time ultrasound and power Doppler) cover the entire parathyroid tumor.
Results
At baseline, serum calcium and iPTH concentrations were above normal range in all patients (2.62–3.34 mmol/l and 66.58–875 pg/ml, respectively). At day 1 after LA serum calcium normalized in 7/11, was under the normal range in 3/11 treated. Serum iPTH was low in 6, normal in 2 and elevated in 3 subjects (2 of them with hypocalcemia). At 3 months after ablation serum calcium and iPTH normalizedin 10/11. In one patient with large parathyroid tumor (3 ml) only partial improvement (decrease of calcium and iPTH concentrations) was achieved. Vocal cord palsy was observed in one of the subjects treated.
Conclusion
LA may be a valuable alternative treatment for patients with primary hyperparathyroidism and high surgery or anesthetic risk.

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AEP129

The picture of primary hyperparathyroidism in Italy: Proceeding from hyperparanet survey

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This is a multicentre retrospective observational study, with the aim to characterize the presentation, management and cure rate of Primary Hyperparathyroidism (PHPT) in Italy. Sixty-one Italian Centres of Endocrinology participated in the study. Clinical, biochemical and instrumental records of 2173 patients with diagnosis of PHPT were collected on a specific online platform (Hyperparanet). Patients were 1808 females (83.2%) and 365 males (16.8%). Diagnosis of PHPT was made at the same centre which followed the patient in 1888 cases (86.9%). PHPT was sporadic in the majority of patients ($n=2044$ patients, 94%), in the remaining a familial form was diagnosed including 69 cases of MEN1, 34 cases of FIHP, 3 of HPT-JT, 2 MEN2A and 20 cases of FHH. The age at diagnosis was 61 ± 15 in the whole group and 45 ± 15 in familial patients. Clinical manifestation of the disease were: nephrolithiasis (either symptomatic or imaging detected) in 687 patients (31.6%), osteoporosis (T score <–2.5 at any site) in 1071 patients (49.2%) complicated by clinical fragility fractures in 282 cases (12.9%), symptoms of hypercalcemia in 104 patients (0.04%). Neuropsychiatric symptoms were detected in 244 (11.2%) cases and cerebrovascular accidents in 60 (0.02%). Only 432 patients were considered completely asymptomatic according to the latest guidelines. Mean serum calcium adjusted for albumin was 12 ± 0.1 mg/dl, PTH 129 ± 117 pg/ml, 25OHD 33 ± 20 ng/ml, 24-hours urinary calcium 291 ± 117 mg, without significant differences between sporadic and familial patients. Parathyroid imaging was performed in all centres in the majority of patients, independently of the indication for surgery. Ultrasound was positive in 833/1414 (58.9%), MIBI scintigraphy in 646/1143 (56.5%) and imaging was concordant in 638 cases. 689 (31.7%) underwent parathyroidectomy, performed at the same centre in half of the cases. At histology a single parathyroid adenoma was found in 554/689 cases (80.4%), a double adenoma in 36 (0.05%), a multiglandular disease in 48 (0.07%), an atypical adenoma in 16 (0.02%), a parathyroid carcinoma in 17 (0.02%). In 18 cases no parathyroid tissue was found at neck exploration. The rate of cure was 88.9: a persistence of the disease occurred in 71 cases and recurrence in 5 cases. Seven cases of persistence/recurrence occurred in

familial forms, the remaining cases in apparently sporadic disease. PHPT is a common endocrinopathy in Italy, presenting mostly as a sporadic disease, still burden by common even if silent bone and kidney involvement. The cure rate in patients who undergo parathyroidectomy is high, in centres with parathyroid surgery experience.

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AEP130

Phase II study of the impact of AZD4017, a selective 11β-HSD1 inhibitor, on osteocalcin in post-menopausal osteopenia

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The causative link between circulating glucocorticoid excess and osteoporosis is established. Although circulating cortisol levels do not change significantly with age, local tissue metabolism may be implicated in age-related bone loss. The enzyme11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) increases local cortisol production, is expressed in human osteoblasts and its activity increases with age leading to a decrease in bone formation. We hypothesised that selective 11β-HSD1 inhibition may enhance post-menopausal bone formation. A UK phase II randomised, double-blind, placebo-controlled trial of 90 days treatment with AZD4017 (a selective 11β-HSD1 inhibitor) was conducted across 2 centres. 55 post-menopausal women with osteopenia on bone density criteria were recruited. Participants received 400 mg twice daily of oral AZD4017 (active) compared to matched placebo over 90 days. The primary outcome measure was impact of AZD4017 on the bone formation marker, osteocalcin. Secondary objectives included correlation with 11β-HSD1 activity, safety, tolerability and reversibility. Baseline characteristics (age, BMI, blood pressure, bone density, cortisol secretion or metabolism) were matched between the active and placebo groups. At 90 days absolute osteocalcin measurements did not differ between active group (mean (SD): 22.3 (SD 8.59) ng/ml, $n=22$) versus placebo (21.7 (SD 9.21) ng/ml, $n=24$). Similarly, linear regression analysis of osteocalcin at 90 days adjusted for baseline osteocalcin demonstrated an estimated treatment effect of 0.95 (95% CI (–2.69, 4.60), not significant). Selective 11β-HSD1 inhibition was inferred through a large reduction in the urinary [THF+alloTHF]/THE ratio at 90 days (active group (mean 0.1 (SD 0.12), $n=19$) versus placebo (mean 0.6(SD 0.26), $n=22$). This returned to baseline by 180 days. Importantly urinary free cortisol/cortisone ratio as a surrogate marker of 11β-HSD2 activity, was unchanged at 90 days (estimated treatment effect –0.054 (95% CI (–0.21, 0.10)). 5α/5β reductase activity was also unchanged (estimated treatment effect –0.19 (95% CI (–0.34, –0.039)). Linear regression analysis of osteocalcin adjusted for change from baseline at 90 days in 11β-HSD1 activity, suggests that degree of 11β-HSD1 inhibition was a poor predictor of osteocalcin at 90 days. This phase II randomised controlled trial demonstrates that AZD 4017 selectively inhibits 11β-HSD1 activity *in vivo* in a safe and reversible manner. However, at 90 days there is no treatment effect on bone formation as measured by osteocalcin. Therefore, the relative impairment of bone formation in post-menopausal women, is not improved by changes to the intracellular production of cortisol, at least in subjects with normal glucocorticoid levels.

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AEP131

Changes in the relative expression of circulating microRNAs linked to bone metabolism in HIV-infected Individuals with low bone mass

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Objective
Human immunodeficiency virus (HIV)-infected patients demonstrate an increased risk of osteoporosis and fractures. The pathophysiology of HIV-induced bone loss is complex and remains largely unknown. Recent studies have identified a molecular signature of small non-coding RNAs (microRNAS) in patients with osteoporosis, but data are lacking in HIV-infected patients. The aim of the present study was to investigate the expression profile of microRNAs related to bone metabolism in HIV infected (HIV+) patients with osteoporosis.
Methods
This was a cross-sectional study of one single centre. Thirty HIV+ male patients on anti-retroviral treatment (ART) with low bone mass and 30 male HIV+ patients matched for age and ADT duration with normal bone mass were included in the analysis. Twenty matched for age not –HIV infected (HIV-) and otherwise healthy individuals, from whom 10 had low bone mass and were drug-naive at the time of enrollement were also included as controls. All participants had measurements of bone mineral density, vertebral fracture assessment and complete biochemical work up. In our study cohort we evaluated changes in the serum relative expression of selected miRs linked to bone metabolism.
Results
Mean age of the enrolled HIV+patients and mean duration of ART were 55 ± 8 years and 11 ± 7 years, respectively. None of the participants had a prior history of a fragility fracture. Three miRs were significantly deregulated in HIV+ patients with osteoporosis compared to HIV+patients with normal bone mass. In particular miR-24 was significantly increased (fold change 2.34, $P=0.03$), and miR21 and miR-23a were significanlty decreased (fold changes 0.49, $P<0.001$ and fold change 0.75, $P=0.04$, respectively). The relative expression of miR-124 was significantly decreased (fold change 0.432, $P=0.02$) in the serum of HIV+patients compared to controls. In a subgroup analysis between osteoporotic patients with and without HIV-infection, the relative expression of miR-124 and miR-29a were also significantly decreased in the serum of HIV+ patients compared to HIV- individuals (fold regulation 0.12, $P=0.01$ and fold regulation 0.07, $P=0.02$)
Conclusion
The serum expression profile of miRs linked to bone metabolism is significantly deregulated in HIV+ osteoporotic males compared to HIV+ patients with normal bone mass, in line with what has been shown in non HIV infected osteoporotic patients.

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Denosumab associated risk of malignancy- systematic review and meta-analysis of randomized controlled trials

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Context
Possible increased risk of malignancy in patients treated with denosumab has been concerned due to inhibition of the immune modulator receptor activator of nuclear factor κ-B ligand.
Objective
To assess the risk of malignancy associated with denosumab treatment.
Data Sources
PubMed and Cochrane Central Register of Controlled Trials were searched up to May 27, 2019.
Study Selection
All randomized controlled trials of denosumab (60 mg every 6 months) versus any comparator. Trials using higher drug doses for prevention of skeletal-related events were excluded.

Data Extraction
Data were independently extracted by two reviewers. We used a fixed effect model to pool risk ratios (RR) with 95% confidence intervals (CI).
Data Synthesis
Twenty-five trials (21,523 patients) were included. The risk of malignancy was comparable between denosumab and other comparators (absolute risk difference 0%, RR 1.08 [95% CI, 0.93–1.24], I2=0%). Sensitivity analysis based on adequate allocation concealment showed similar results. The risk of malignancy did not differ between groups in any of the subgroup analyses, including stratification by race, individual comparators, indications for treatment and longer drug exposure (≥ 24 months, 9 studies). The risk ratio of cancer-related death was comparable between groups.
Conclusions
Early concerns about a potential increased risk of malignancy resulting from an immune modulatory effect of denosumab are not supported by evidence from 25 RCTs with drug exposure of up to 48 months.

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AEP133

Prevalence and determinants of radiological vertebral fractures in a cohort of patients with Klinefelter syndrome

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Klinefelter syndrome (KS) is a frequent form of male hypogonadism that may be associated with a series of comorbidities potentially affecting quality of life and survival. As a matter of fact, KS was shown to negatively impact skeletal health. However, the studies so far published on this topic were mainly focused on evaluation ofbone mineral density (BMD) and bone microstructure, whereas data on fracture risk are still lacking. In this cross-sectional study, we evaluated for the first time the prevalence and determinants of vertebral fractures (VFs), i.e. the hallmark of osteoporosis, in KS. Eighty-seven patients with KS(mean age 41 years, range 18–64) were consecutively evaluated for radiological VFs (by quantitative morphometry) and lumbar spine and femoral neck BMD (by DXA). Fifty KS patients with age ≥40 were also evaluated by the Fracture Risk Assessment (FRAX) tool. Seventy-three patients were undergoing testosterone replacement therapy (TRT; 45 with testosterone undecanoate, 25 with transdermic formulation and 3 with testosterone enanthate). Seventy-four patients were taking vitamin D (cholecalciferol and calcifediol in 54 and 20 patients, respectively; 17 patients in combination with calcium). Low BMD was found in 22 patients (12 with osteopenia, 3 with osteoporosis and 7 with "low BMD per age"), whereas no one resulted to be at increased risk for either major (> 10%) or hip fracture (>3%) by the FRAX algorithm. Thirteen patients presented VFs with a median spine deformity index (SDI) of 2 (range 1–9). Prevalence of VFs was similar between normal vs low-BMD patients (15.9% vs 13.6%; $P=0.80$). Noteworthy, patients with VFs had significantly higher age at diagnosis of KS as compared to patients who did not fracture (33 years, range 15–47 vs 20 years, range 0–48; $P=0.03$), without significant differencesin age at the time of observation ($P=0.16$), body mass index ($P=0.25$), TRT ($P=0.43$), vitamin D therapy ($P=0.43$), calcium supplementation ($P=0.69$) and serum testosterone levels ($P=0.34$). Moreover, patients with VFs were more likely to complain back pain in comparison to those without VFs (33.3% vs 7.4%; $P=0.03$). In conclusion, this study provides a first evidence that KS may be associated with high risk of VFs in close relationship with delay in disease diagnosis and independently of BMD values and serum testosterone levels. Moreover, the association between VFs and back pain would suggest that VFs may have a clinical impact in KS, such as already reported in patients with primary male osteoporosis

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AEP134

Radiofrequency Echographic Multi Spectrometry (REMS) evaluation in patients with primary osteoporosis and primary hyperparathyroidism

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Background
Radiofrequency Echographic Multi Spectrometry (REMS) is a new ultrasound-based tool for bone mineral density (BMD) measurement, recently approved by FDA for the use in clinical routine to diagnose osteoporosis (OP) and to monitor bone changes. However, data on patients with secondary OP are not available. The aim of our study was to compare REMS and DXA ability in identifying clinical (cFX) and morphometric vertebral fractures (VFx) in patients with primary OP (pOP) and with primary hyperparathyroidism (PHPT).
Methods
We enrolled 99 consecutive postmenopausal women referred to our Unit for pOP ($n=52$) or PHPT ($n=47$), who underwent REMS, DXA and spine X-ray to detect possible VFx. We excluded subjects with history ofbone-active therapy. The same operator executed REMS lumbar spine (LS) and total femural (TF) scan in all patients.
Results
Age, body mass index and BMD at any site, prevalent cFX (18.6% and 20.8%, respectively, $P=0.793$) and VFx (21.4% and 22.4%, respectively, $P=0.907$) were comparable between pOP and PHPT. The concordance between DXA and REMS in diagnosing osteopenia or OP was below 70% and comparable in pOP and PHPT patients (LS 64% and 58%; TF 66% and 51%, $P=$ns for all comparisons). The prevalence of OP according to REMS (REMS-OP) was lower than according to DXA (DXA-OP), although not significantly, in both pOP and PHPT groups (26.9% and 65.4%, $P=0.06$; 28.6% and 64.3%, $P=0.103$ respectively). Altogether, patients with DXA-OP had a higher prevalence of all (cFX+VFx) fractures (42.4% and 21.4%, $P=0.05$) and a trend for a higher prevalence of VFx (28.8% and 10.7%, $P=0.06$, respectively) as compared with patients without DXA-OP. Conversely, patients with and without REMS-OP had a similar prevalence of all fractures (32.0% and 39.1%, $P=$ns) and VFx (20.0% and 23.4%, $P=$ns). Similar results were obtained in both groups. Considering both the whole sample and the pOP and PHPT patients separately, REMS and DXA values were significantly associated, however the strength of correlation was low (LS all $r=0.373$, $P=0.001$; LS pOP $r=0.371$, $P=0.008$; LS PHPT $r=0.389$, $P=0.14$; TF all $r=0.48$, $P=0.001$; TF pOP $r=0.435$, $P=0.02$; TF PHPT $r=0.544$, $P=0.001$; respectively).
Conclusions
In our real life study, REMS seems to overestimate BMD values compared to DXA in both pOP and PHPT patients. REMS reliability in identifying patients with both cFx and VFx, seems to be lower than DEXA, in both pOP and PHPT patients. Future studies are needed to understand how to optimize this however promising technique.

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AEP135

Melatonin affects hypoxia-stressed cardiomyocyte differentiation of mouse embryonic stem cells

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Hypoxia causes oxidative stress and is known to affect cardiovascular dysfunction and the programming of cardiovascular disease. Melatonin is the hormone released primarily from the pineal gland and has been proven to be an antioxidant. Melatonin promotes the expression of antioxidant enzymes such as superoxide dismutase and catalase. To confirm the effect of hypoxia on the differentiation of mouse embryonic stem cells (mESCs) into cardiomyocytes, hypoxia condition induced during the differentiation period. mRNA expressions of cardiac-lineage markers (*Brachyury, Tbx20, and Ctn1*) decreased at differentiation 2-10day. The expression of hypoxia marker, Hif-1α, was increased in the hypoxia condition-plus mESC differentiation 2–10,

6–10, and 2–10 day, but melatonin receptor *Mtnr1a* mRNA expression was reduced in the hypoxia condition-plus mESC differentiation 6–10 and 2–10 day. To confirm the effect of melatonin against the hypoxia condition, melatonin was treated. Beating ratio and the mRNA expression of cardiac-specific marker (*Ctn1*) restored in 500 μM melatonin-plus hypoxia condition. The level of Hif-1α protein decreased in melatonin (100, 500 μM)-plus hypoxia, but the *Mtnr1a* mRNA expression was increased. In these conditions, the expressions of p-ERK and Bax proteins decreased, but the levels of p-Akt, PI3k, and Bcl-2 proteins increased. Melatonin has been shown to mitigate hypoxia via the ERK pathway in the differentiation of mESCs into cardiomyocytes. The expression of *Mtnr1a* mRNA was increased during the differentiation of mouse stem cells into cardiomyocytes, indicating that melatonin may affect cardiomyocyte differentiation. These results suggest that melatonin may protect against hypoxia in cardiomyocyte differentiation of mouse embryonic stem cells.

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AEP136

Hypercalcaemia in pregnancy due to parathyroid adenoma – would you recognise it?

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Introduction
Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder in the general population, with a prevalence of 0.1 to 0.4%, caused by a solitary parathyroid adenoma in 80 to 85% of cases. In pregnancy, however, it is rare and usually manifests with non-specific symptoms leading to the delay in diagnosis A 33-year-old female patient who wasreviewed in obstetrics clinic at 15/40 weeks gestation. She complained of body aches, intermitted nausea and vomiting, and feeling generally unwell. She visited her GP who performed blood tests including serum bone and thyroid profiles. This revealed a high adjusted serum calcium of 3.27 millimoles/litre (mmol/l), borderline-low phosphate of 0.79 mmol/l, a high PTH of 9.4 pmol/L, and normal vitamin D level at 83. Thyroid profile showed a free T4 (FT4) level of 35.1 pmol/l and a suppressed thyroid-stimulating hormone (TSH) of less than 0.01 mU/l. 24-hour urine calcium result was elevated at 11.1 millimoles. She was admitted to the hospital and was managed conservatively with IV fluids. She was also started oncarbimazole 5 mg daily. The calcium level improved after IV hydration to 2.88 mmol/l and discharged home. Three weeks later,a repeat blood test showed persistent hypercalcaemia of 2.96 mmol/l andsymptomatic requiring admission for IV hydration. Initial neck ultrasonography was performed and did not show parathyroid adenoma. It did however detect a total of three benign-appearing nodules in both lobes of the thyroid gland. The patient also underwent urinary tract ultrasonography and nephrolithiasis was ruled-out. She had parathyroictomy at 19th week of gestation, after which calcium and PTH levels returned to normal. The patient did not suffer from any post-operative complications.
Discussion
Primary hyperparathyroidism in pregnancy(PHPT) rare and probably underdiagnosed. This is partly due to the large overlap between symptoms of hypercalcaemia and symptoms commonly attributed to pregnancy itself, such as nausea and vomiting. It is necessary to recognise symptoms of hypercalcaemia, when present, during pregnancy and establish the diagnosis of primary hyperparathyroidism to prevent both foetal and maternal complications associated with hypercalcaemia.
Conclusion
Serum bone profile is not routinely performed during pregnancy check-ups; however, we would highly recommend screening for primary hyperparathyroidim in the presence of any symptoms known to be associated with hypercalcaemia. This would lead to early diagnosis Diagnostic and therapeutic options are more limited for PHPT in pregnancy than in the non-pregnant patient. Parathyroidectomy is strongly advised as a first-line curative measure,in the second trimester.

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Are young primary hyperparathyroidism patients differ from older ones regarding clinical and biochemical features?

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Introduction
Primary hyperparathyroidism (PHPT) is a prevalent endocrinologic disease and the most common cause of hypercalcemia. PHPT usually affects the elderly. PHPT younger than 40 years of age is less frequent. In young patients especially for ones younger than 30 years of age, screening for familial syndromes such as MEN 1 and MEN 2A is recommended. However, in most of the cases genetic tests are negative and evidence for other endocrine components are absent. Herein this study we retrospectively evaluated the data of 322 patients with asymptomatic PHPT patients who were operated and compared the biochemical and clinical features of young patients (<40 years old) with older ones.
Method
This study had a retrospective design. We evaluated the data of the patients who admitted to our university hospital's endocrinology clinics and diagnosed with PHPT between September 2015-may 2018. According to the clinical guidelines all symptomatic patients and asymptomatic ones who had at least one indication for surgery were operated. There were 346 adenomas belonging to 322 patients in total. The patients were classified into 2 groups regarding age (<40 years or >40 years old as Group 1 and 2, respectively). Two group was compared according to clinical, biochemical and histopathologic features.
Results
There wasn't any statistically significant difference between groups according to histopathology (adenoma, hyperplasia and carcinoma) ($P=0.065$). In both groups there was female predominance, but number of male patients was significantly higher in Group 1 compared to Group 2 ($P=0.004$). Serum Ca levels were similar whereas PTH level was higher in Group 1. According to ultrasonographic features, Group 2 had higher prevalence of accompanying thyroid nodules or thyroiditis ($P<0.001$).Interestingly T scores on femur and total vertebra and prevalence of osteoporosis were similar in between two groups. The percentage of preoperative localization with US and mean size of adenomas were similar. However positive result on MIBI scan was higher in Group 2. median Urinary Ca excretion was higher in Group 1 despite similar vitamin D levels ($P=0.0012$).
Conclusion
The phenotype of PHPT in young adults is different from older patients. In our cohort number of male patients, serum PTH, urinary Ca excretion were higher in younger patients.

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A new and valuable predictor for the diagnosis of primary hyperparathyroidism: Ca/P Ratio

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Introduction
Primary hyperparathyroidism (PHPT) is a common endocrine disorder that is characterized by hypercalcemia and elevated or normal levels of parathyroid hormone (PTH). Most PHPT cases are incidentally discovered when routine laboratory analysis reveals hypercalcemia. PHPT should be considered in any person with elevated serum calcium (Ca) levels and no clear evidence of malignancy. Serum phosphorus (P) is low due to the phosphaturic effects of PTH and mostly in the lower half of the normal range. As serum Ca and P are inversely related in PHPT, we examined the diagnostic value of the serum Ca/P ratio in the diagnosis of PHPT.
Method
A total of 364 patients followed at our clinic with a diagnosis of PHPT were retrospectively analyzed. As a control group, we selected 98 patients who attended the clinic in the same time period, presenting serum PTH, Ca and P within the normal range. The main outcome measures were: serum Ca, P, albumin, PTH, 25-OH vitamin D and creatinine. Both patients with normocalcemic PHPT and hypercalcemic PHPT were included. The diagnostic accuracy of Ca/P was investigated using receiver operator

characteristic (ROC) curve analysis. The resultant cut-off was verified using the independent set of data containing 100 patients and 50 control cases.
Results
There were 317 (87%) females and 47 (13%) males in patients group, and the mean age of the cohort was 53.9±11.4 years (range: 20–82). Ca and PTH were significantly higher in PHPT than in controls ($P<0.0001$). The Ca/P ratio was also significantly higher in PHPT than in controls ($P<0.0001$). ROC curves analyses identified a cutoff value as 3.23 (mg/dl) for Ca/P ratio with a sensitivity and specificity of 94% and 93%, respectively ($P<0.0001$). This cut-off value was confirmed by an independent group of cases (100 PHPT and 50 control cases) with 91% sensitivity and 80% specificity.
Conclusion
Ca/P is a precious predictor for the diagnosis of PHPT and it can be used instead of evaluating serum Ca and P levels solely. As Ca/P ratio is easily accessible and inexpensive, it will be useful for PHPT diagnosis and provide simplicity especially for thepractitioners with limited resources.

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AEP139

Comparative efficacy of parathyroidectomy and conservative management in patients with mild primary hyperparathyroidism: A systematic review and meta-analysis of randomized-controlled studies

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Objective
Whereas parathyroidectomy (PTx) has an established benefit in patients with symptomatic primary hyperparathyroidism (PHPT), its efficacy in patients with mild (asymptomatic) PHPT has not been proven. The aim of this study was to systematically investigate and meta-analyze the best available evidence from randomized-controlled trials regarding the efficacy of PTx on fracture risk (primary endpoint), as well as bone mineral density (BMD), serum calcium concentrations, nephrolithiasis risk and quality of life (QoL) (secondary endpoints) compared with conservative management (non-PTx; pharmaceutical intervention or active surveillance) in patients with mild PHPT.
Methods
A comprehensive literature search was conducted in PubMed, Scopus and Cochrane, from conception to January 11th, 2020. Data were expressed as percentage mean differences with 95% confidence intervals (CI). The I2 index was employed for heterogeneity.
Results
Five studies (four with active surveillance, one with etidronate) fulfilled the eligibility criteria [334 patients, mean age 66.5±5.6 years, mean follow-up time 25.2 (range 6–60) months]. There was no difference in fracture incidence between non-PTx and PTx patients [relative risk (RR) for total fractures 2.93 (95% CI 0.91, 9.49), I2=0%; RR for vertebral fractures 5.66 (95% CI 0.68, 47.31), I2=0%; RR for non-vertebral fractures: 1.32 (95% CI 0.31, 5.67), I2 not applicable)]. Lower BMD values were demonstrated in non-PTx compared with PTx patients [mean difference in lumbar spine BMD –4.53% (95% CI –6.25, –2.81), I2=98%; femoral neck BMD -2.89% (95% CI -5.71, –0.06), I2=100%; total hip BMD –3.44% (95% CI –5.49, –1.39), I2=99%; forearm BMD: no difference]. With respect to serum calcium concentrations, PTx patients demonstrated a mean reduction of 10.8% (95% CI 9.1, 12.6, I2=98%) compared with non-PTx patients. No difference was observed between the groups in the risk for kidney stone formation or the QoL indices (physical and social function, physical and emotional role function, mental health, vitality and bodily pain; general health higher in the non-PTx group).
Conclusions
PTx is not a first-line treatment option in patients with mild PHPT, as it does not improve fracture, nephrolithiasis risk or QoL, compared with conservative management; however, PTx does improve BMD and serum calcium concentrations.

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AEP140

Prevalence of hypoparathyroidism in the EU: A systematic review and meta-analysis

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Background
Hypoparathyroidism (HP) is caused by a group of heterogenous conditions that result in deficient secretion of parathyroid hormone. Due to this heterogenous nature, information on HP prevalence is highly variable and studies can be difficult to compare. This study aims to estimate the true prevalence of HP within the EU via comparison of available literature and analyses of sub-populations.
Methods
MEDLINE and EMBASE were systematically searched for peer-reviewed English-language studies involving population-based European HP prevalence estimates. Studies were assessed for rigor of methodology, suitability of study population, and were also reviewed for possible biases. In total, five prospective studies qualified via these criteria and were comprehensively evaluated for estimates of HP prevalence. Some studies presented prevalence results based on less stringent criteria than others, thus wherever possible criteria were standardized across studies, and where necessary, prevalence results were reevaluated. In addition, any estimates of temporal and geographical trends across the EU were collected.
Results
The most common division within adult HP is between non-surgical and post-surgical cases. All resulting data from the qualifying studies were entered into separate meta-analyses for both non-surgical and post-surgical HP. Based on these analyses the best prevalence estimate for non-surgical HP in the EU was 1.2/10,000 (95% CI : 0.6–1.6 per 10,000) and the best prevalence estimate for post-surgical HP in the EU was 2.0/10,000 (95% CI : 1.6–2.3 per 10,000). To evaluate temporal trends, use was made of detailed information available in the literature regarding change in rates over time. Post-surgical HP has been increasing at a faster rate (growth of approximately 0.03 cases per 10,000 annually) than non-surgical HP (growth of approximately 0.01 cases per 10,000 annually).
Conclusions
The overall prevalence of HP in the EU was estimated at 3.2 per 10,000 population in 2020 with a growth rate of approximately 0.04 cases annually. Although study criteria and geographies of the included studies were disparate, once separated into non-surgical and post-surgical, results were more consistent. These results help inform the epidemiology of both non-surgical and post-surgical HP within the EU.

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AEP141

Identifying clinical characteristics of hypoparathyroid patients in turkey: The 'HIPOPARATURK-NET Study'

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Hypoparathyroidism is a rare endocrine disorder whose epidemiologic characteristics regarding the cause, clinical course, acute and chronic complications have not been well defined. There is also a substantial geographic variability regarding those parameters, and country-specific local data is scarce. This study was conducted to assess the baseline characteristics, including the demographics, etiologic distribution, disease severity, medications used, frequency of acute and chronic complications, and treatment/follow-up patterns of patients with chronic (>6 months) hypoparathyroidism in Turkey.

The 30 centers that participated in the study filled out the data of their registered adult hypoparathyroid patients, retrospectively, through detailed questionnaires using their patient records. Overall, 738 hypoparathyroid patients were included in the analysis. The mean age of the patients was 48.5±13.3 years, and the majority were female (83.9%). The most common etiology of hypoparathyroidism was surgical damage to the parathyroid gland (postsurgical group; $n=661$, 89.6%) following a complete/partial thyroidectomy, parathyroidectomy and/or neck dissection with an indication of Graves disease in 31 (5.5%), multinodular goiter in 282 (49.6%), thyroid cancer in 155 (27.3%) and toxic nodular/multinodular goiter in 100 (17.6%). The nonsurgical cohort included 77 (10.4%) patients. The patients had a mean disease duration of 9.5±6.9 years. The majority ($n=593$, 81.6%) were diagnosed shortly after the operation that caused hypoparathyroidism while 19 (2.6%) patients had a diagnosis since childhood, another 89 (12.2%) were diagnosed as outpatients with mild symptoms of hypocalcemia, 18 (2.5%) withemergency department admission due to hypocalcemic tetany, and 8 (1.1%) were asymptomaticduring the routine blood tests that led to the diagnosis. Of all patients in our cohort, 117 (15.9%) had serum calcium measurements <7.5 mg/dl, 111 (15.1%) between 7.5–8.0 mg/dl, 200 (27.1%) between 8.0–8.5 mg/dl, 304 (41.3%) between 8.5–10.5 mg/dl and 5 (0.7%) >10.5 mg/dl under their current treatment. The postsurgical and the nonsurgical groups did not differ in terms of age, BMI, and duration of disease. The nonsurgical group had a lower nadir plasma PTH concentration than the postsurgical group (2.28±2.77 vs 10.08±7.92, $P<0.0001$) while their current daily dose of calcitriol and corresponding serum calcium levels on treatment were similar. In conclusion, the etiology of hypoparathyroidism is predominantly surgery-induced in our cohort. Most patients are under 1–2 times yearly follow-ups, and their serum calcium levels are in an acceptable target range. Rates of screening for chronic complications are below desired levels and need to be improved.

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AEP142

The prevalence of postoperative (PO) chronic hypoparathyroidism (HypoPTH) in bilbao, northern spain

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Introduction
HypoPTH is an uncommon disorder, mostly due to anterior neck surgery. The prevalence of HypoPTH has been studied in surgical series and registries, (USA, Denmark and Hungary) where only a minority of patients has HypoPTH due to non-surgical causes. In Spain data on PO HypoPTH in endocrinologist clinical practice has been published recently. The aim of this study was to establish the prevalence of chronic PO HypoPTH in Bilbao area, with a population 2019: 346,843.
Subjects and methods
In Spain, patients who have been prescribed a drug in the public Health Service are recorded in a regional prescription database. Data were obtained by searching for patients on both calcitriol and levothyroxine between 2012 and 2019. For all identified patients the individual medical record was reviewed. Only patients who underwent neck surgery (mainly total thyroidectomy) were included in the study. For the analysis, chronic PO HypoPTH was defined as hypocalcaemia with inadequate low PTH levels following neck surgery that necessitated treatment with calcitriol for more than 1 year.
Results
436 out of 489 patients met inclusion criteria. 110 patients were found to have chronic POHypoPTH, giving a prevalence of 31.7/100,000 inhabitants. Among patients operated on in our center before 2012, 56 developed chronic HypoPTH. No data is available on the total number of surgeries performed during this period of time. 119 thyroid surgeries performed before 2012 are on record. 63/119 patients develop transient HypoPTH. Some of them were taking calcitriol although calcium and PTH levels were normalized. Between 2012 and 2019, 1096 patients underwent thyroid surgery (1,021 total thyroidectomy, 214 central/lateral lymphadenectomy additionally) in our center. Among those, 317 (31%) resulted in HypoPTH, with 269 (26.3%) of these cases being transient, and 48 (4.7%) chronic.
Conclusion
– The estimated prevalence of chronic PO HipoPTH in the population of Bilbao is similar to other areas related in the literature.
– The prevalence of PO hypoPTH in our center since 2012 is high 31% but in line with other surgical series, being chronic in 4.7%.
– No differences were found between surgeries for benign or malignant disease.
– Data published in endocrinologist clinical practice show higher rates: 48.3% transient and 14.5% chronic. These differences are due to the methodologies used.
– Although recovery from chronic HypoPTH is rare, patients should be monitored forserum PTH levels so that unnecessary treatments can be avoided.

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Osteocalcin may participate to the bone-parathyroid crosstalk through activation of the calcium-sensing receptor in human parathyroid adenomas

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Parathyroid glands regulate bone metabolism through PTH, while bone modulates parathyroid function through calcium and FGF23. Bone releases the matrix protein osteocalcin (OC), whose hormone function is increasingly evident. We tested the hypothesis that OC may modulate parathyroid function. The 6 hours-stimulation of human parathyroid cells derived from adenomas (PAds) ($n=5$) with γ-carboxylated OC (GlaOC; 40–60 ng/ml) increased the expression levels of the *PTH*, *CASR* and *CCND1*genes, as well as of WNT/β-catenin member *AXIN2*. In PAds-derived cells ($n=4$), GlaOC (60–80 ng/ml) incubation for 10 min, inhibited the basal phosphorylated ERK/total ERK ratio (pERK/ERK) and increased the basal phosphorylated AKT/total AKT ratio (pAKT/AKT) and active β-catenin. PhosphoERK/ERK, pAKT/AKT and active β-catenin were similarly modulated by the incubation with 60–80 ng/ml undercarboxylated OC (GluOC). OC is known to exert its biologic effects through the activation of the putative membrane receptor GPRC6A. GPRC6A transcripts and proteins were variably detected in human PAds ($n=10$). Immunohistochemistry showed specific GPRC6A cytoplasmic staining in some cells and membrane staining in other cells scattered throughout the parenchyma, both in normal and tumor parathyroids. Immunofluorescence detected colocalization of GPCR6A with PTH and GCM2. GPCR6A is a homolog of the calcium sensing receptor (CASR). CASR was variable expressed in the present series of PAds and it did not correlate with the GPRC6A expression. We investigated whether OC activates CASR, using HEK293 cells transiently transfected with GPRC6A (GPRC6A-HEK293) and with CASR (CASR-HEK293). Increasing GlaOC and GluOC (20–80 ng/ml) induced significant increases of pERK/ERK, decreases of pAKT/AKT, while active β-catenin was unaffected in GPRC6A-HEK293 cells. By contrast, GlaOC and GluOC inhibited the basal pERK/ERK levels and increased basal pAKT/AKT in CASR-HEK293 cells, resembling the effects detected in PAds-derived cells and suggesting that OC activates CASR in parathyroid cells. These patterns of response to OC were observed in presence of 1.5 mM extracellular calcium ($[Ca^{2+}]_o$). When CASR-HEk293 cells were cultured in presence of 5.0 mM $[Ca^{2+}]_o$, pERK/ERK levels were inhibited by GluOC, but not by GlaOC. By contrast, in $[Ca^{2+}]_o$-deprived medium, basal pERK/ERK levels were unaffected by both GlaOC and GluOC in both PAds-derived and CASR-HEK293 cells, while GlaOC and GluOC reverted their stimulatory effects on pERK/ERK, exerting inhibitory effects in GPRC6A-HEK293 cells, consistent with modulation of the biologic effects of OC by $[Ca^{2+}]_o$. These new data add OC to the bone-parathyroid cross-talk and suggest that CASR can be activated by OC with different intracellular signaling responses depending by $[Ca^{2+}]_o$.

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Long-term effectiveness of asfotase alfa in adults with pediatric-onset hypophosphatasia in routine clinical practice

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Hypophosphatasia (HPP) is a rare, inherited, metabolic disorder caused by deficient tissue-nonspecific alkaline phosphatase activity. A heterogeneous presentation in adults includes musculoskeletal symptoms, impaired physical function, and reduced health-related quality of life (HRQoL). Asfotase alfa is the only approved treatment for pediatric-onset HPP. We evaluated, in a real-world setting, the long-term effectiveness of asfotase alfa on physical function and HRQoL among adults with pediatric-onset HPP (NCT03418389). Data were analyzed from adults who had pediatric-onset HPP, were aged >18 years, and received care at the Orthopedic Institute of the Julius-Maximilians-University of Würzburg. They had received asfotase alfa for ≥24 months. Physical function evaluation included the 6-Minute Walk Test (6MWT), Timed Up-and-Go (TUG) test, Lower Extremity Functional Scale (LEFS), and Short Physical Performance Battery (SPPB). HRQoL was assessed with the 36-item Short-Form Health Survey, version 2 (SF-36v2); prevalence and intensity of pain were evaluated. Safety data were collected throughout the study. The study included 14 (11 women, 3 men) patients, with a median (min, max) age of 53 (20, 78) years for women and 46 (19, 57) years for men at asfotase alfatreatment initiation. All 14 patients had compound heterozygous *ALPL* gene variants, ≥1 HPP bone manifestation, and history of ≥1 fracture. We previously reported on the score changes for each tool from baseline to 12 months; here we report changes from 12–24 months. Improvements on treatment were observed over the first 12 months and maintained over another 12 months. Median (min, max) distance, according to 6MWT, was similar at 12 (320 [0, 605] m) and 24 (316 [60, 600] m) months ($n=13$; $P=0.115$). A slight increase in median time to complete the TUG test from 11.3s–13.75s was not statistically significant ($n=7$; $P=0.382$). Specific SPPB component results were stable. Slight decreases seen in median 4m usual gait speed from 1.12 m/s–1.02 m/s ($n=9$; $P=0.61$) and in median repeated chair rise time from 12.53 s–12.48 s ($n=8$; $P=0.398$) were not statistically significant. Improvements in LEFS ($n=10$) and SF-36v2 Physical Component Summary ($n=9$) scores were observed early at 3 and 6 months and remained stable over 24 months. Changes in pain level ($n=5$) were variable between 12 and 24 months. No new safety signals were identified. These data suggest adults who have pediatric-onset HPP treated with asfotase alfa in real-world settings have marked improvements in clinical and functional outcomes, which were observed early and sustained over 24 months of treatment.

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Prevalence of osteoporosis, vertebral fractures and hypogonadism in HIV-infected men.

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With HAART (Highly Active Anti-Retroviral Therapy) introduction, HIV infection history has radically changed. Increased survival has led to new complications, including osteoporosis. The pathogenesis of osteoporosis in HIV patients is multifactorial: virus, HAART, smoking, alcohol, physical inactivity, comorbidities, and hypogonadism can interact in bone depletion. Aim of this study was to evaluate the prevalence of osteoporosis, vertebral fractures (VF) and hypogonadism in 189 HIV men. Spine and femoral mineral density (BMD) were acquired by DXA. Vertebral fractures were assessed by quantitative morphometric analysis; VF were defined as mild, moderate and severe based on a height ratio decrease of 20–25%, 26–40% and more than 40%, respectively. For the assessment of gonadal status, total testosterone (TT), calculated free testosterone (cFT), SHBG, LH and FSH values were obtained. Hypogonadism was defined as overt with low TT or cFT levels, and classified in primary, secondary or normogonadotropic based on LH levels. The prevalence of subclinical hypogonadism (TT and cFT normal values, with high LH levels) was assessed. Possible risk factors, and bone turnover markers levels were also collected. Osteoporosis was found in 32.8% of patients (62/189), 30.2% (57/189) showed at least one VF, 11.1% (21/189) had an overt hypogonadism, and 9.5% (18/189) subclinical hypogonadism. Among the patients with overt hypogonadism, 4 showed a primary form, 2 secondary and 12 normogonadotropic. Compared to non-osteoporotic patients, those with osteoporosis had longer infection duration (17.9 vs 13.6 y, $P=0.0034$), had been on HAART for more years (14.6 vs 10.9, $P=0.0049$), and showed higher SHBG values (78.9 vs 64.5, $P=0.049$). With respect to VF, years of HIV-positivity (18.2 vs 13.6, $P=0.0028$), HAART duration (14.7 vs 10.9, $P=0.0056$), SHBG (84.2 vs 62.7, $P=0.0092$) and FSH (12.01 vs 8.21, $P=0.049$) values differed significantly between fractured and non-fractured patients. No significant difference was found between hypogonadal and eugonadal patients in terms of BMD (0.954 vs 0.968), vertebral T-score (–1.8 vs –1.5) and VF (29.4% vs 27.2%), whereas it was achieved for BMI (26.3 vs 24.7, $P=0.017$) and FSH (15.4 vs 7.7, $P<0.001$). This study included a large number of HIV+ men in which testicular function was fully assessed, in contrast to most of the published studies. These data show a high prevalence of osteoporosis, VF and hypogonadism in HAART treated HIV-infected men. The role of hypogonadism in osteoporosis and VF pathogenesis is unclear, even if a correlation between FSH and SHBG levels and skeletal fragility was found in these patients.

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Bone metabolism in patients with extreme insulin resistance (IR) syndromes

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Introduction
Diabetes is associated with increased fracture risk both in patients with type 1 (T1D) and type 2 diabetes (T2D) despite differences in bone mineral density BMD (decreased in T1D and increased in T2D). In T2D, insulin resistance (IR) is selective, with some insulin signaling pathways impaired, while others are overactive due to hyperinsulinemia. It is not clear how different insulin signaling pathways might contribute to the bone phenotypes observed in diabetes. To understand the role of insulin signaling in bone metabolism, we studied patients with severe impairment of all insulin signaling pathways (insulin receptor, INSRmutation) versus severe, selective IR (lipodystrophy, LD). *We hypothesized*differences in insulin signaling in INSR vs LD might lead to differing bone phenotypes.
Patients and methods
116 LD and 27 INSR. BMD of the spine, total hip (TH), femoral neck (FN), and 1/3 radius by DXA (age 18–30y); kidney ultrasonography; PTH, serum calcium, phosphorus, magnesium, alkaline phosphatase, osteocalcin, vitamin D 25-(OH), vitamin D 1,25-(OH), HbA1c, and 24-hour calcium excretion were analyzed.
Results
There were no difference in HbA1c in INSR vs LD. BMD was higher in LD vs INSR at the spine (1.167±0.06 vs 0.808±0.07, $P<.001$), TH (1.120±0.08 vs 0.783±0.07, $P<.001$) and FN (0.986±0.08 vs 0.687±0.05, $P<.001$). No difference was found in 1/3 forearm. Kidney stones and nephrocalcinosis were found in 40 and 46.7% of INSR vs 0% and 2.2% of LD patients ($P=.0001$).
Conclusion
Similar to T1D vs T2D, patients with severe IR due INSR mutation vs lipodystrophy have opposing phenotypes for BMD (low in INSR, high in LD) and renal calcium deposition (high in INSR, normal in LD). These findings are consistent with a model in which insulin action in bone is needed to

prevent bone resorption. In the absence of insulin signaling (INSR), there is increased bone resorption, thus increasing Ca filtration by the kidneys and causing renal Ca deposition. In the selective IR with hyperinsulinemia due to LD, enhanced insulin signaling in bone prevents bone resorption, leading to high BMD. Fracture risk for our patients has not been established, thus the clinical significance of the differences in BMD is not known. Further research is needed to clarify the long-term effect of insulin signaling on bone and mineral metabolism.

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AEP147

Core muscles trainig for muscle strength improvement in patients with osteoporotic compression vertebral fractures

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Aim
To estimate the effect of new complex physical rehabilitation program on core muscles strength in patients with osteoporotic vertebral fractures (VFs).
Materials and methods
Study comprised of 90 osteoporotic patients aged 50–80 (65.4±9.1 years) with low-traumatic VFs who were randomized as 2:1 into intervention group (group1, $n=60$) and control group (group2, $n=30$). Patients in group1 received an intensive rehabilitation course including back muscle training with mechanical loads #10; sensorimotor training on double unstable platform #10; kinesohydrotherapy in a pool #15; physical exercises in a gym #10. Group2 was prescribed only physical exercises in a gym #15. All patients undergo tenzodynamometry on BackCheck diagnostic unit (Dr. Wolff, Germany) at baseline, at the end of rehabilitation course and in a month after the rehabilitation as follow-up.
Results
After a rehabilitation course muscle strength increased significantly in trunk extensors (TE) from 15.8±10.1 to 21.7±13.1 kg ($P<0.0001$), trunk flexors (TF) from 14.5±9.1 to 18.9±10.2 kg ($P<0.001$), left lateral flexors (LLF) from 12.8±7.2 to 17.5±9.6 kg ($P<0.01$) and right lateral flexors (RLF) from 13.2±7.1 to 17.8±9.2 kg ($P<0.01$). The maximal improvement of muscle strength was registered in TF +6.5±57.5% above recommended values ($P<0.001$). TE strength deficiency significantly decreased ($P<0.001$), but did not reach the recommended values –15.8±25.8%. After the 1-month follow-up muscle strength in all examined muscles didn't significantly diminished vs results just after rehabilitation course completion ($P>0.05$). The strength of all the studied muscles were higher ($P<0.01$) and the muscle deficiency was less in TE ($P<0.05$) and TF ($P<0.001$) in group1 vs group2 in a month of follow-up after rehabilitation course.
Conclusions
A new complex physical rehabilitation program leads to increase of muscle strength and elimination of muscle strength deficiency in patients with osteoporotic VFs, and these effects are not attenuate for at least a month after the treatment completion.

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AEP148

Successful quantification of symptom load by a disease-specific questionnaire HPQ 40/28 and analysis of influencing biochemical parameters in patients with postsurgical hypoparathyroidism

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In hypoparathyroidism (HypoPT), patients suffer severely from reduced quality of life. The complexity of HypoPT demands a disease-specific control instrument to characterize symptom load. We employed a newly developed disease-specifichypoparathyroid patient questionnaire (the HPQ 40/28) to investigate and quantify HypoPT patients' complaints and contributing factors. In this cross-sectional, two-center study, patients with postsurgical HypoPT ($n=49$) were matched for sex and age and compared to patients having undergone thyroid surgery without HypoPT (ThySu, $n=39$)) and patients with primary hyperparathyroidism (pHPT, $n=35$). The HPQ 40/28 was filled in when patients visited the respective center. Clinical background information, blood tests,as well as current medication were documented by the physician. Serumcalcium laywithin the reference range in 87% of HypoPT patients, serumphosphate in 95.7%, and calcium-phosphateproduct in 100%. HPQ 40/28 scores for the scales "pain and cramps" (PaC), "neurovegetative symptoms" (NVS), "numbness or tingling", and "heart palpitations" were significantly elevated in comparison with control groups. Correlations between complaints and laboratory parameters could be demonstrated in the HypoPT group, with serumcalcium correlating with NVS ($r=0.309$, $P<0.05$) and serumphosphate with loss of vitality ($r=0.349$, $P<0.05$). Calcium-phosphate product was the main contributor to symptom load with an influence on PaC ($r=0.295$, $P<0.05$), loss of vitality ($r=0.498$, $P<0.001$), numbness or tingling ($r=0.328$, $P<0.05$), and memory problems ($r=0.296$, $P<0.05$). In conclusion, the newly developed HPQ 40/28 successfully identified and quantified symptoms typical in HypoPT patients. Using the HPQ 40/28, the calcium-phosphateproduct was identified as the predominant factor in the severity of complaints in HypoPT

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AEP149

Investigation of total- and free-25OHD levels by different methods in pregnant women

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Avoiding vitamin D deficiency can be beneficial in prevention of adverse maternal, fetal and neonatal outcomes. Because of increasing level of vitamin D-binding protein (DBP) in pregnancy, the determination of free-25OHD should be required, whose adequate measure is a challenge for the analytics. Literature data are contradictory whether total-or free-25OHD fraction is more reliable taking into consideration the methods of measurement. Data of publications on free or total, bioavailable 25OHD are quite discrepant. Our study started in connection with gestational diabetes (GDM) we aimed to evaluate the correlation of 25OHD-fractions measured by different assays.
Methods
88 sera of pregnant women (31.4±5.0 years; gestational age: 26.6±1.3 weeks; out of them 25 suffered from GDM; 62 cases were on 665±742 IU_D3/day) were investigated. Measured biochemical markers were: calcium, t-25OHD by three methods; liquid chromatography/mass spectrometry (t-25OHD_MS) chemiluminescence immunoassay (t-25OHD_CLIA, Liaison, DiaSorin) and protein binding assay (t-25OHD_PBA, Cobas Roche), as well as albumin and DBP (immunoturbidimetry Roche and Dako, Integra, Modular) to calculate free levels (c-f-25OHD_MS; c-f-25OHD_CLIA ; c-f-25OHD_PBA). Direct measured free-25OHD (dm_f-25OHD) was determined by ELISA (DiaSource, Future Diagnostics) method. To evaluate the agreement of different methods Passing & Bablok regression and Bland & Altman analysis were used.
Results
The levels of t-25OHD_MS were significantly higher ($P<0.001$) than the routinely used methods (MS: 76±31 vs CLIA: 59±24; PBA: 60±25 nmol/l;

both biases: -24%). Tests of linearity were excellent (MS-CLIA: $P=0.939$ and MS-PBA $P=0.634$). Mean of dm-f-25OHD level was lower compared to c-f-25OHD_MS (7.5±2.1 vs 8.3±3.2 pmol/L; $P<0.05$; bias:-5.3% and linearity: $P=0.808$).But the c-f-25OHD_CLIA and c-f-25OHD_PBA levels are lower (both: 6.5±2.1 pmol/l; $P<0.01$;) than dm_f-25OHD. The biases of both methods are: +18%; the linearities with dm_f-25OHD are by CLIA: $P=0.934$ and by PBA method: $P=0.634$. The markers of 25OHD didn't show any significant differences between GDM and GDM-negative cases.

Conclusion

Our results confirm the acceptable dissimilarity of the routinely, frequently used methods (CLIA and PBA). They diverge from LC-MS method but show an excellent linearity with that. It should be recommended to define cut-off points depending on assay method for monitoring vitamin D supply in pregnant women. Unfortunately, we have few data to suggest to the sole measure of free-25OHD. Although our results indicate that calculated free levels are not consistent because the one underestimated, the other two overestimated the direct measured levels.

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AEP150

Analysis of 25OHD levels in chronic renal failure depending on the methods

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Vitamin D deficiency is common in patients with chronic renal failure (CRF) based on routinely determined total-25-hydroxyvitaminD (t-25OHD) levels. The present knowledge is contradictory whether the direct measured free-25OHD (dm_f-25OHD) or the calculated free-25OHD (c_f-25OHD) is the best indicator of the vitamin D supply for CRF patients. Adding methods to our previously described first experiences on this subject, in this study we aimed to serve newer data to make this question clearer.

Method

95 patients [39 men; 56 women; 69±12 years: 30 on peritoneal dialysis (PD) 34 on haemodialysis (HD), both on 3000 IU D_3/day; 31 pre-dialysis (preD) on 1400 IU D_3/day] were investigated. Their sera were analysed for vitamin D-binding protein (DBP) (Dako), albumin (immunoturbidimetry, Integra), Ca, PTHi (Roche) dm_f-25OHD (ELISA, FutureDiagnostics), t-25OHD [using two methods: liquid chromatography/mass spectrometry (t-25OHD_MS) and chemiluminescence immunoassay (t-25OHD_CLIA; DiaSorin]. The c_f-25OHD levels were calculated from both t-25OHD (c_f-25OHD_MS; c_f-25OHD_CLIA). Differences between the methods were evaluated by Passing&Bablok regression and Bland & Altman analysis.

Results

Albumin levels were the lowest (PD:33±4 vs HD:37±4; preD:39±4 g/l; $P<0,001$) and DBP concentrations the highest (PD:351±39 vs HD:307±48 mg/l; $P<0,001$) in PD group. The t-25OHD_CLIA levelswere lower compared to t-25OHD_MS t-(73.4±22.4 vs 106.2±30.5 nmol/l; $P<0,0001$) in all groups, but the greatest bias was in PD patients (37%; test of linearity: $P=0.660$). Free 25OHD levels obtained by calculation were overestimated compared to dm_f-25OHD concentrations in all three groups (all groups: dm_f-25OHD: 13.2±4.5 vs c_f-25OHD_MS: 26.4±11.4 and c_f-25OHD_CLIA: 20.0±8.2 pmol/l; $P<0.001$). The negative biases were significantly higher in case of c_f-25OHD_MS in all groups compared to c_f-25OHD_CLIA (preD: –53% vs –35,2%; PD: –67% vs –31%; HD: –45% vs –66%) but the test of linearity showed the best correlation between direct measured and c_f-25OHD_MS in PD ($P=0,999$). All 25OHD fractions were significantly lower ($P<0,010$) in PD compared to HD (t-25OHD_CLIA:73.4 vs 94.8 nmol/l; t-25OHD_MS:106 vs 122 nmol/l; dm-f-25OHD: 11.9 vs 14.9 pmol/l; c_f-25OHD_CLIA:24.2 vs 31.3 pmol/l) though the patients received the same dose of vitamin D3. Out of the five obtained 25OHD levels only dm_f-25OHD showed significant positive correlation ($r=0.39$) with Ca and only in preD patients.

Conclusions

Our results highlight that determination of cut-off values that reflect the appropriate vitamin D supply should be defined according to the diseases and the methods as well. Calculated free levels overestimate the 25OHD supply. The dm_f-25OHD promises to be the most reliable marker in preD. All five methods certify that patients on PD need much higher doses of cholecalciferol.

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AEP151

Cardiovascular status in chronic hypoparathyroidism – a single-center analysis in 133 patients compared to the general german population

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Introduction

Even though it is well known that long-term complications, such as renal insufficiency and brain calcifications can occur in patients with hypoparathyroidism (HPT), the risk of cardiovascular diseases still remains unclear.

Objective

To perform a systematic assessment of cardiovascular function in a well-characterized cohort of patients with HPT compared to population-based controls.

Methods

133 patients with chronic HPT (disease duration >6 months) were included and systematically examined regarding cardiovascular comorbidities. All participants were assessed by blood pressure measurement, electrocardiogram (ECG), cardiac ultrasound and laboratory analyses. We performed 1:3 propensity score matching with individuals from the German population-based Study of Health in Pomerania (SHIP-TREND, $n=2682$) for age, sex, body-mass-index, smoking status, diabetes mellitus, dyslipidemia and TSH. Group differences were tested with Wilcoxon signed rank sum test (continuous variables), McNemar-test (dichotomous variables) or Friedman's Chi-Square test (categorical variables).

Results

Patients with HPT showed significantly higher diastolic blood pressure levels than controls (median 86 mmHg vs 78 mmHg, $P<0.01$), whereas systolic blood pressure was comparable (126 mmHg vs 127 mmHg, $P=0.19$). Intake of diuretics (24% vs 6%, $P<0.01$), calcium channel blockers (13% vs 6%, $P<0.01$), as well as angiotensin receptor antagonists (36% vs 27%, $P<0.01$) was significantly more frequent in patients with HPT. QTc intervals were markedly prolonged in HPT patients (438 ms vs 423 ms, $P<0.01$) in ECG. Interestingly, cardiac ultrasound revealed significantly lower interventricular septum thickness (0.8 cm vs 1.0 cm, $P<0.01$), as well as lower E/A ratio (1.0 vs 1.1, $P<0.01$) in HPT. Left ventricular ejection fraction was comparable between patients and controls ($P=0.05$). Regarding valvular dysfunctions HPT patients less frequently presented with insufficiencies of the mitral (20% vs 40%, $P<0.01$) and aortic (1% vs 7%, $P<0.01$) valve, whereas aortic stenosis was more prevalent in HPT compared to controls (7% vs 1%, $P<0.01$).

Conclusion

Here we report more frequent treatment with calcium channel blockers and angiotensin receptor agonists, as well as higher diastolic blood pressure in HPT patients compared to matched controls. Furthermore, QTc intervals remain prolonged in HPT despite established replacement therapy which should be taken into account when treating patients with compounds additionally prolonging QTc. Cardiac ultrasound revealed comparable left ventricular ejection fraction, thinner interventricular septum, as well as lower E/A ratio. Additionally, prevalence of aortic stenosis was higher in HPT, most likely due to valvular calcification. In general, HPT is not associated with striking cardiovascular disease burden in our cohort compared to matched controls.

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AEP152

Renal complications in chronic hypoparathyroidism – a german single-center analysis in 169 patients

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Introduction
Although long-term complications such as nephrocalcinosis and renal insufficiency are well-known in chronic hypoparathyroidism (HPT), standardized investigations of their prevalence and causes are still lacking.
Objective
To systematically investigate the prevalence of renal calcifications and dysfunction and their predictors in a well-characterized cohort of patients with HPT.
Methods
Cross-sectional assessment of comorbidities in 169 patients with chronic HPT (disease duration >6 months). Further examinations included renal ultrasound and laboratory analysis of serum- and urine samples. Logistic regression analysis with backward selection was performed to identify risk factors for the development of nephrocalcinosis.
Results
Out of 169 patients (55±13 yr, 76% female, disease duration 17±15 y), 88% had postoperative HPT. Prevalence of eGFR <60 ml/min/1.73m^2 was 21%, hypercalciuria 29%. Significant correlation between 24-h urine calcium excretion and spot urine calcium (r=0.61, P<0.0001) was observed. Renal ultrasound performed in 151 patients revealed renal calcifications in 9%, nephrocalcinosis in 7% and calculi in 3%. Significant differences between patients with renal calcifications (defined as nephrocalcinosis and nephrolithiasis) and without were found for 24-h urine calcium excretion (8.4±5.9 mmol/d vs 6.1±3.9 mmol/d, P<0.05), albumin-corrected serum calcium (2.1±0.2 mmol/l vs 1.99±0.2 mmol/l, P<0.02), serum phosphate (1.2±0.3 mmol/l vs 1.3±0.2 mmol/l, P<0.05) and serum magnesium (0.73±0.08 mmol/l vs 0.78±0.07 mmol/l, P<0.02). In contrast, no significant difference was found for prevalence of renal dysfunction and eGFR<60 ml/min/1.73 m^2, serum calcium-phosporus product, serum 25-hydroxyvitamin D, 24 h urine calcium-to-creatinine ratio, daily calcium intake or duration of disease (24±20 y vs 16±14 y). In logistic regression analysis only serum calcium could be identified as potential risk factor, in contrast to 24-h urine calcium, serum phosphate, disease duration, as well as dosage of calcium and active vitamin D.
Conclusion
Here we report a high prevalence of eGFR <60 ml/min/1,73 m^2 and hypercalciuria but a low prevalence of renal calcifications. This reduction of eGFR is independent of type of HPT, daily calcium intake and disease duration. In our study, only fasting serum calcium represented a risk factor for the development of nephrocalcinosis. Further studies are warranted to elucidate the pathomechanism behind nephrocalcinosis in patients with HPT.

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AEP153

Risk of fractures in primary hyperparathyroidism: A systematic review and metaanalysis

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Background and objective
An increased risk of fractures in Primary Hyperparathyroidism (PHPT) has been reported in a number of relatively small studies. Performing a systematic literature search we identified available studies and calculated common estimates by pooling results from the individual studies in a meta-analysis.
Methods
Searching EMBASE and PubMed using both free text word search and Mesh terms we identified published studies reporting the risk of fractures in PHPT compared to a control group or compared to the expected fracture rates from the general population. We calculated odds ratio (OR) with 95% confidence interval (CI).
Results
A total of 804 studies were identified of which 13 studies and a total number of 5457 PHPT patients and 13633 controls were included. Overall, risk of any fracture was increased compared to controls (OR 2.01; 95% CI, 1.61–2.50; I^2 46%, 5 studies). Analysis of fracture risk at specific sites showed an increased risk of fracture at the forearm (OR 2.36; 95% CI, 1.64–3.38; I^2 0%, 4 studies) and spine (OR 3.50; 95% CI, 1.66–7.89; I^2 87%, 10 studies). Risk estimate for hip fractures was also increased although non-significantly (OR 1.27; 95% CI, 0.97–1.66; I^2 0%, 3 studies). Risk of vertebral fractures (VFx) was also increased if analyses were restricted to only studies with a healthy control group (OR 5.76; 95% CI, 3.86–8.60; I^2 29%, 6 studies), studies including only patients with mild PHPT (OR 4.22; 95% CI, 2.20–8.12; I^2 57%, 4 studies), or studies including only postmenopausal women (OR 8.07; 95% CI, 4.79–13.59; I^2 0%, 3 studies).
Conclusions
Overall, PHPT is associated with an increased risk of fractures. Although number of studies are limited – it seems that the risk is increased across different skeletal sites including patients with mild PHPT. Of notice, relative risk of VFx seems to be extraordinarily high in postmenopausal women.

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AEP154

Psychiatric Comorbidities in Chronic Hypoparathyroidism – a German Single-Center Analysis in 107 Patients

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Introduction
Reduction of quality of life in patients with chronic hypoparathyroidism (HPT) has been reported by several studies. Additionally, self-report data point to a higher prevalence of anxiety disorders in HPT compared to patients after thyroidectomy.
Objectives
To characterize psychiatric diseases in a systematically reviewed cohort of patients with chronic HPT.
Methods
We systematically assessed psychiatric comorbidities in a well-characterized cohort of patients with chronic HPT (n=107) using standardized questionnaires (depression: Patient Health Questionnaire (PHQ9), Beck Depression Inventory (BDI2), anxiety: State-Trait Anxiety Inventory (STAI)) and further performed a diagnostic interview using the Mini-DIPS (n=103).
Results
Out of the 103 interviewed patients 69% were female. 72% presented with postoperative HPT. The STAI provides a screening tool to assess both state (X1) and trait (X2) anxiety separately. Scores range from 20–80 with higher scores being positively correlated with higher levels of anxiety. In the STAI X1 21% of the patients scored between 40 and 50 and 25% of patients had a score above 50 (mean 40±13). Regarding trait anxiety (STAI X2) 24% of patients had values between 40 and 50, whereas 20% scored above 50 points (mean 39±12). In contrast, most patients with chronic HPT did not show markedly elevated scores in PHQ9 (81% with scores below 9), as well as BDI2 (72% with scores below 13). No significant correlations could be observed between serum calcium, parathyroid hormone or 25-OH-Vitamin D levels and scores of STAI X1, X2 and PHQ, whereas BDI2-scores significantly correlated with serum calcium levels (Pearson's r=0.386, P<0.001). In the diagnostic interviews, anxiety disorder was found in 36% of patients. The kinds of anxiety disorders according to the Mini-DIPS were: Agoraphobia (31%), specific phobia (21%), panic syndrome (16%), generalized anxiety disorder (16%), social phobia (10%), and posttraumatic stress disorder (9%).
Conclusion
The performance of systematic screening as well as diagnostic interview for psychiatric disorders in HPT showed a high prevalence of anxiety disorders despite established treatment of HPT. However, the pathophysiology still remains unclear.

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AEP155

Do near-infrared intra-operative findings by the use of indocyanine green correlate with post-thyroidectomy parathyroid function? - the ICGPREDICT study

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Background/Aims
Post-operative hypoparathyroidism still remains a significant complication after thyroidectomy. Intraoperative imaging modalities, such as near infrared fluorescence by the use of indocyanine green (ICG), may assist to identify and preserve the parathyroid glands (PGs). The purpose of this study was to test the association between intra-operative ICG staining scoring system and 24-h post-operative parathyroid hormone (PTH) levels, as well as its capability of intra-operative PG identification.
Methods
This was a prospective study, recruiting patients scheduled for total thyroidectomy by the same surgical team, from December 2018 to April 2019. Intraoperative angiography was performed, after infusion of ICG solution (5 mg). Two minutes later, images were acquired by the near-infrared system.
Results
Sixty patients fulfilled eligibility criteria. The percentage of temporary post-operative hypoPT (defined as PTH <14 pg/ml) was 11.66%. No association between intra-operative ICG staining score (expressed as the number of PGs scoring <2 per patient) and 24-h post-operative PTH ($r=0.011$, $P=0.933$) or serum calcium concentrations ($r=0.127$, $P=0.335$). There was also no correlation between the location of PGs scoring ≤2 and post-operative PTH ($P=0.257$) or serum calcium levels ($P=0.950$). Moreover, with regard to secondary endpoint, ICG correctly identified parathyroid glands in 98.3% of cases. ICG score was not affected by age, gender, duration of operation or thyroid gland pathology. No allergic reactions attributed to ICG administration were observed.
Conclusions
Intra-operative ICG staining scoring system did not predict 24-h post-operative PTH and serum calcium levels. This modality does not seem to assist in intra-operative parathyroid identification during a total thyroidectomy.

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AEP156

DXA scanning in primary hyperparathyroidism: Should forearm DXA be performed routinely?

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Introduction
Primary hyperparathyroidism (PHPT) is a disease associated with a decrease in bone mineral density (BMD), especially in cortical bones such as distal radius. Therefore, the BMD measurement of forearm is valuable in the detection of cortical bone loss by PHPT. However, forearm measurement is not routinely recommended for the diagnosis of osteoporosis in PHPT. In this study, we aimed to evaluate the importance and priority of forearm BMD measurement in PHPT.
Material and Methods
286 (249 female/37 male) patients with PHPT and eGFR>60 ml/min, whose BMD was measured at lumbar spine, femur and forearm by dual-energy X-ray absorptiometry (DXA) wererecruited to the study. The patients were divided into two groups as group 1 ($n=139$) with forearm osteoporosis and group 2 ($n=147$) without forearm osteoporosis. Age, sex, creatinine, eGFR, alkaline phosphatase (ALP), corrected calcium, phosphorus, magnesium, parathormone, 25 OH vitamin D, 24-hour urine calcium levels were recorded and compared between the groups. Additionally, patients with osteoporosis at any site, forearm osteoporosis, and the other two regions were normal but only with forearm osteoporosis were evaluated as three groups. The effect of the isolated forearm osteoporosis on surgical criteria was evaluated in patients without other surgical indications.
Results
The mean age at diagnosis of PHPT was 55.9±12.1 years. Our patients in group 1 were older than in group 2 ($P=0.001$). 151 (53%) patients have osteoporosis at any site, 139 (49%) have forearm osteoporosis, and only 76 (27%) patients have osteoporosis at forearm while the other two sites were normal. ALP, corrected calcium and parathormone levels in group 1 were significantly higher than patients in group 2 ($P=0.005$, $P=0.005$, $P<0.001$, respectively). The groups were similar in terms of other variables. Only the isolated forearm osteoporosis was determined as the surgical indication in 22 patients who did not meet any other surgical criteria. In the light of these findings, additional operation indication was established by evaluating the forearm BMD in 7% ($n=22/286$) patients of the study group.
Conclusion
Although forearm BMD measurement is not routinely recommended in patients with PHPT, only spine and femur evaluation may not be adequate since cortical bone loss is more expected in this disease course. In our study, the frequency of diagnosis of osteoporosis and operation indication increased with BMD measurements, including forearm site. Therefore we suggest forearm BMD measurement to be performed routinely in PHPT.

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AEP157

Burden of illness in patients with chronic hypoparathyroidism not adequately controlled with conventional therapy: A survey of physicians in belgium and the Netherlands

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Patients with hypoparathyroidism are at risk of short-term and long-term complications and comorbidities, such as renal, cardiovascular, metabolic or cognitive manifestations. The purpose of this study was to determine the burden of illness (BOI) in patients with not adequately controlled chronic hypoparathyroidism receiving conventional therapy (oral calcium supplements and active vitamin D) in Belgium and the Netherlands. Data werecollected from a cross-sectional, 2-part online survey for which all endocrinologists from the two countries, and nephrologists from Belgium, were invited by telephone to participate. Part 1 included collecting data on general management of patients with hypoparathyroidism. In part 2, physicians were requested to provide data of ≤2 unique cases of patients with chronic hypoparathyroidism not adequately controlled on conventional therapy. Data collected included aetiology of hypoparathyroidism, clinical manifestations, comorbidities, results of laboratory and other investigations used for diagnosis and screening for complications, therapy received, and physician's perception of impaired quality of life (QoL) rated on a visual analogue scale. A total of 93 physicians - 29 nephrologists and 36 endocrinologists from Belgium and 28 endocrinologists from the Netherlands - provided data for 97 patients treated with conventional therapy (60 cases were from Belgium and 37 from the Netherlands). The average age of patients was 48.5±16.8 years, the majority (66%) were women, and neck surgery (67%) was the most common cause of hypoparathyroidism. At the time of the survey, 96% of patients were receiving calcium supplementation and 97% active vitamin D: 51% alfacalcidol and 46% calcitriol. Mean duration of hypoparathyroidism was 4.5±4.9 years (median, 2.2; range, 0.17–20.00). The majority of patients had neuromuscular (85%) and/or neurological (67%) symptoms,

71% had abnormal biochemical parameters, and 10% were overweight. Most frequently reported comorbidities included hypertension (25%), renal comorbidity (20%), diabetes mellitus (12%), and dyslipidaemia (11%). Amongtreating physicians, 71% subjectively perceived a deterioration in QoL (degree of change, –1.4) in their patients since disease onset. Among patients who were hospitalised in the 12 months before the survey because of inability to control chronic hypoparathyroidism(17%), the median number of hospitalisations was 2.0 with a median duration of hospitalisation of 5.0 days. Patients with chronic hypoparathyroidism not adequately controlled on conventional therapy experienced a substantial BOI, mainly because of persistence of symptoms and presence of multiplecomorbidities. These findings highlight the need for general awareness of the BOI associated with inability to adequately control hypoparathyroidism.
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AEP158

Burden of illness in patients with chronic hypoparathyroidism not adequately controlled with conventional therapy: European subanalysis of a global patient survey

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Although chronic hypoparathyroidism is known to negatively affect health-related quality of life (HRQoL), burden of illness is less well defined in patients whose disease is not adequately controlled on conventional therapy. We report burden of illness for the European subset of a patient survey in 13 countries globally. 398 adults with chronic hypoparathyroidism not adequately controlled on conventional therapy (recruited by treating physician or patient association) completed the survey online anonymously between October 2017 and March 2018. Health status/HRQoL were evaluated using the 36-item Short Form Health Survey version 2.0 (SF-36 v2.0)/EuroQoL 5 Dimensions Five-Level (EQ-5D-5L). Employment status/productivity were evaluated using the Work Productivity and Activity Impairment (WPAI) questionnaire. Symptom severity was self-rated as well as assessed using a hypoparathyroidism symptom diary (7-day recall period). This subanalysis includes 203 patients (Denmark; $n=11$; France, $n=13$; Germany, $n=31$; Italy, $n=35$; Norway, $n=16$; Spain, $n=35$; Sweden, $n=17$; UK, $n=45$). Self-rated symptom severity was mild (25%), moderate (61%), or severe (14%); no one self-reported as symptom-free. Mean SF-36 summary scores (0–100), EQ-5D-5L utility scores (0–1), and EQ-5D-5L visual analogue scale (VAS) scores (0–100) according to self-rated symptom severity are summarised in the Table; health status and HRQoL decreased with increasing self-rated symptom severity. According to the hypoparathyroidism symptom diary tool, moderate/severe/very severe symptoms were reported by 41%/24%/8% of patients for physical fatigue, 43%/12%/2% for muscle cramps, and 48%/13%/1% for heaviness in the limbs; moderate/severe/very severe cognitive symptoms (ie, slow/confused thinking) and mood symptoms of anxiety and sadness/depression were reported by 30%/13%/4%, 31%/14%/1%, and 13%/10%/3% of patients, respectively. Impact on personal relationships, work, sleep, and ability to exercise were reported by 68%, 77%, 83%, and 86% of patients. Mean (SD) percent overall impairment at work score was 51.5% (25.67%) and increased with self-rated symptom severity (Table). These results demonstrate a burden of illness on HRQoL, symptoms, and functioning at work in European patients with not adequately controlled chronic hypoparathyroidism. Degree of burden reflected self-rated symptom severity. These results are consistent with those from the global population.
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Mean (SD)	Mild Symptoms (n = 51)	Moderate Symptoms (n = 121).	Severe Symptoms (n = 28)	Total (n = 203)
SF-36 physical	45.3 (9.28)	37.7 (8.85)	28.7 (7.54)	38.3 (10.09)
SF-36 mental	44.2 (10.15)	35.1 (8.68)	30.1 (10.75)	36.6 (10.41)
EQ-5D-5L utility	0.9 (0.10)	0.7 (0.20)	0.4 (0.27)	0.7 (0.24)
EQ-5D-5L VAS	71.4 (17.76)	56.5 (16.69)	39.6 (16.5)	56.4 (19.33)
WPAI impairment due to problem, %	30.8 (23.72)	54.0 (21.71)	76.6 (16.1)	51.5 (25.67)

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AEP159

Clinical features and management of primary hyperparathyroidism discovered by parathyroid incidentaloma

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Primary hyperparathyroidism (PHPT) is nowadays usually diagnosed as an asymptomatic disease but it might be related with advanced end-organ damage. Parathyroid incidentaloma (PI) is the term describing enlarged parathyroid nodules that are unexpectedly discovered on surgery or by imaging performed for nonparathyroid disorders. The recognition of PI might uncover a clinically significant PHPT with the potential for surgical cure. We retrospectively reviewed patients' records with a newly diagnosed PHPT in the last 5 years in our hospital. Among 74 retrieved patients we found 14 (18.9%) diagnosed with PHPT following the discovery of PI. Nonparametric statistical tests were used for the comparison between this PI PHPT group and the rest of our cohort. Overall thirteen PHPT patients with PIs were discovered on neck ultrasound. The median volume of these PIs was 403.2 mm^3 (117–1570 mm^3). One PI was found during the surgery in a patient referred for thyroidectomy at our institution. The previous presence of PHPT in this case was suggested by development of transitory hypocalcemia due to hungry bone syndrome after the surgery. The rest of PHPT patients were mostly identified by incidental laboratory findings of hypercalcemia (36.5%) or during the osteoporosis work-up (32.4%). The comparison of the PI PHPT group with other PHPT patients found a statistically similar level of PTH, calciuria and eGFR. The highest serum calcium level measured before treatment was lower in PI PHPT patients ($P=0.037$), but rates of normocalcemic PHPT were comparable in both groups. The PI PHPT group had more often positive scintigraphy ($P=0.027$). Differences in the occurrence of osteoporosis and urolithiasis did not reach statistical significance. The PI PHPT group was less likely to meet the international consensus criteria for surgery ($P<0.01$), but the frequency of surgical management did not differ between groups. The surgical cure for PHPT was achieved in all PI PHPT patients and pathohistology of all operated PIs confirmed adenomas. PIs are still an uncommon but relevant way of revealing PHPT. In our institution the radiological suspicion for enlarged parathyroid glands is further investigated only after the positive biochemical screening for parathyroid hyperfunction. This certainly introduces a bias in our clinical data because silent PIs are disregarded, similar to bias which exists in other circumstances of discovering asymptomatic PHPT. We emphasize that all relevant laboratory parameters are checked not to miss the normocalcemic PHPT. An appropriate follow up for suspicious silent nodules should be suggested.

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AEP160

Serum and tissue expression profile of microRNAs that regulate genes related to the pathogenesis of sporadic parathyroid adenomas

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Background
Epigenetic changes appear to be implicated in the development of parathyroid tumors. In this study we investigated the microRNA expression profile in the serum and tissue samples from patients with primary hyperparathyroidism (PHP) due to sporadic parathyroid adenomas (SPAs).
Methods
Our study cohort consisted of 40 patients with PHP due to SPAs that underwent parathyroidectomy (PTX).
MicroRNA extraction was performed from a) 40 FFPE samples of sPA, b) 10 FFPE samples of normal parathyroid tissue (NPT) from patients that underwent total thyroidectomy for benign multinodular goiter, c) serum samples from the 40 cohort patients with PHP at two time points (before and 2 months post PTX), d) serum samples from 10 healthy individuals that served as controls, also at two time points (t1=baseline and t2=2 months after). Nine microRNAs (miRs) were selected based on their interaction with genes related to the pathogenesis of sporadic parathyroid adenomas (namely, miR-17-5p, miR-24, miR-29b, miR-31, miR-135b-5p, miR-186, miR-195, miR-330-3p, and miR-483-3p)
Results
The microRNA expression profile of SPAs at tissue level differed significantly compared to NPT. In particular, the relative expression of 4 miRs, namely miR-17-5p, miR-31, miR-135 and miR-186 was significantly decreased in SPAs compared to NPT (fold change 0.17, fold change 0.034, fold change 0.01 and fold change 0.09, respectively, all P values<0.001). On the other hand, the relative expression of 2 of the tested miRs was significantly increased in SPAs (miR-24, fold change 12.4, $P<0.001$; miR-29b, fold change 18.5, $P=0.011$). Similar to the microRNA profile in the tissue the relative expression of miR-135 was also significantly decreased in the serum of patients with PHP compared to controls (fold change 00.7, $P<0.001$), while no significant differences were found in the serum of PHP patients before and after parathyroidectomy.
Conclusion
MicroRNAs that regulate genes linked to the pathogenesis of SPAs, such as menin 1 (miR-24 and miR-29b), cyclin D1 (miR-17-5p) and CaSR (miR-31 and miR-135) are significanlty deregulated in SPA samples compared to NPT, suggesting a role for epigenetic changes in the development f SPAs.

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AEP161

The use of PET/CT with 11C-methionine for the diagnosis of a patient with renal hyperparathyroidism

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Background
Renal hyperparathyroidism (rHPT) may affect up to 30% of dialysispatients with end-stage renal disease (ESRD). rHPT is associated with an increased risk of cardiovascular events (CE) and bone diseases such as pain or renal osteodystrophy. Total or subtotal parathyroidectomy may be a chance to reduce the severity of the symptoms and decrease the risk of CE and death. Pre-operative scintigraphy and ultrasound diagnostics in rHPT may be insufficient at even up to 60% of the patients. PET/CT examinationusing the new tracers may be helpfulto localize parathyroid glands in such cases.
Clinical Case
We present the case of a 46-year-old woman with ESRD who underwent a kidney transplant in 2002, in whom ESRD relapsed in the mechanism of chronic antibody mediated graft rejection. Patient was on dialysis since 2014. Time of dialysis was 12 hours per week and the dialysis was adequate. Due to persistent high level of PTH, the occurrence of pathological fracture of the tibia, and presence of the brown tumors of the pelvic bones, the patient received cinacalcet (90 mg/d). During cinacalcet treatment minimal concentration of PTH was 1223 pg/ml and patient reported bone and joints pain, fatigue and pruritus. US of the neck and parathyroid scintigraphy with ^{99m}Tc-MIBI revealed no pathological features. In February 2019 PET/CT with ^{11}C-methionine (^{11}C-MET) was performed, showing high tracer accumulation in the left lower parathyroid gland and in the numerous brown tumors of the ribs. In June 2019 patient underwent subtotal parathyroidectomy and parathyroid adenoma in histopathology examination was reported. On the first day after the surgery PTH serum level drop to 236 pg/ml, but then started to rise again till 823 pg/ml and hypocalcemia occurred. Hungry bone syndrome (HBS) was suspected. Patient received calcium oral supplementation and 6-week post-operative follow-up ^{11}C-MET PET/CT examination revealed no foci of pathological marker accumulation in the parathyroid glands what allowed to exclude rHPT recurrence, giving confirmation of the HBS. Significant reduction in the size and number of brown tumors in the bones was observed additionally. Eight weeks after surgery, the PTH concentration was 281 pg/ml with normocalcemia and slightly elevated phosphate concentration, and the patient reported a significant improvement in well-being.
Conclusion
1. ^{11}C-MET PET/CT examination was a useful tool for setting best surgical treatment and postoperative follow up of a patient with rHPT
2. The HBS after successful surgical treatment of rHPT can be a potent parathyroid stimulating factor and mimic rHPT recurrence.

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AEP162

Oncogenic osteomalacia – from diagnosis to recovery in 7 days

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Introduction
Oncogenic Osteomalacia (OO) is a rare paraneoplastic syndrome, resulting from fibroblast growth factor 23 overproduction. The rarity of the disease and nonspecific symptoms often cause delay in diagnosis by months, or even years. There are two cornerstones in the diagnostic process. The first concerns clinical identification, where awareness of this uncommon ailment combined with hypophosphatemia and clinical signs may be sufficient to identify OO. The second involves imaging procedures to anatomic localisation of the tumor, which can be complicated as the lesions are usually small, and may occur at various sites.
Aim
We present a case of OO where the whole diagnostic process and treatment took one week, in a patient misdiagnosed during the previous three years. We would like to emphasise that such a fast diagnosis is possible without sophisticated imaging tools. Awareness of this rare disease, coupled with conscientious physical examination can be enough for diagnosis, resulting in efficient treatment.
Materials and methods
Day 1. Physical examination and clinical features:
Patient's main complaints included severe bone pain, general fatigue, muscle weakness, as she required walking assistance. Upon physical examination she exhibited a waddling gait, had pain on palpation of the bones and joints; a flat, cohesive lesion in the subcutaneous tissue in the region of the right scapula was notable.
Day 2. Laboratory diagnosis:
Mild hypophosphatemia and increased activity of alkaline phosphatase were documented (FGF-23 and 1,25(OH)2D3 in process).
Day 3. Imaging diagnosis and surgery:
Soft tissue US of the right scapula region revealed subcutaneous tissue 21x6x27mm, with heterogeneous decreased echogenicity, smooth contours, and increased vascularity.

Surgical removal of the lesion in the right scapula region was performed.
Day 4. Observation:
Neither clinical nor biochemical improvement was noticed.
Day 5. Discharge from the hospital:
MR of the whole body was planned as part of out-patient diagnosis continuation.
Day 7. Histopathological result:
Phosphaturic mesenchymal tumour with small fusiform cells, which focally undergo chondroblastic-like differentiation.
Gradually, phosphate increase and alkaline phosphatase decrease were observed; subsequently the patient began to walk without aid, the waddling gait ceased, general fatigue and pain ended.
Conclusion
By presenting this case we would like to remind clinicians about OO as a rare cause of hypophosphatemia. Prompt diagnosis and treatment can prevent a patient from becoming disabled. Based on our experience, we assume that removing easily accessible lesions before performing sophisticated imaging studies for its localization should be recommended.

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AEP163

Case report: Refractory hypercalcemia due to a pancreatic neuroendocrine tumor misdiagnosed as adenocarcinoma

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Background
Hypercalcemia is a well-described paraneoplastic manifestation encountered in a variety of malignancies. However, it is rarely the initial feature of a neuroendocrine tumor.
Herein we report a caseof metastatic pancreatic neuroendocrine tumor (NET)presenting with a refractory hypercalcemia and initially misdiagnosed as an adenocarcinoma of the pancreas.
Objective
The aim of this case report is to illustratesome of thecomplexities pertaining to the diagnosis of a pancreatic NET and the challenges in the management of an associated hypercalcemia caused by parathyroid hormone related protein (PTHrP) hypersecretion.
Clinical case and results
A 67-year-old woman presented with asthenia and weight loss and was found to have severe hypercalcemia. Laboratory evaluation demonstrated high calcium levels associated with low serum parathyroid hormone (PTH) levels. Despite an initial low PTHrP level, nephrogenous cAMP was elevated consistent with PTHrP related hypercalcemia. Work up revealed a pancreatic tumor associated with liver and splenic metastases but no bone metastases. Biopsy of the liver metastasis concluded to an adenocarcinoma and appropriate chemotherapy was initiated. Despite the stability of the pancreatic tumor, the associated hypercalcemia was refractory to various supportive therapy and chemotherapeutic regimens including corticosteroids, bisphosphonates, calcitonin and denosumab. Because of the indolent progression of the tumor and in view of the persistent hypercalcemia, slides of the pancreatic tumor were reviewed, and complementary immunohistochemistry was performed. The results contradicted the initial diagnosis and were compatible with a well differentiated pancreatic NET. Additional staining was positive for PTHrP confirming the secretion of this hormone by the tumor. Chemoembolization of the liver metastases was performed and treatment with somatostatin analogues (SSA) was introduced allowing a good but transient control of the hypercalcemia. This phenomenon of tachyphylaxis, occurring after a few months of therapy with SSAs, has been described in some patients with NETs. Due to the rise of calcium levels, the patient was referred for vectorized internal radiation therapy.
Conclusion
We report a case of pancreatic NET with hypercalcemia as a presenting feature initially misdiagnosed as adenocarcinoma. Hypercalcemia was refractory to all symptomatic therapies and was transiently controlled with SSA. This case highlights the challenges in diagnosing and controlling hypercalcemia due to PTHrP hypersecretion in patients with NETs. Furthermore, it underlines the importance of reconsidering the initial diagnosis in front of an unusual course of the disease.

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AEP164

Increasing incidence of parathyroid carcinoma according to russian registry of the primary hyperparathyroidism

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Introduction
Parathyroid carcinoma (PC) occurs in 0.005% of all malignant tumors and in less than 1% in primary hyperparathyroidism (PHPT), but recent reports indicate increasing incidence of PC.
Aim
To estimate the prevalence of PC in Russia and to identify its distinctive characteristics relevant as preoperative markers.
Material and methods: We conducted a retrospective study based on the on-line Russian Registry of 3061 patients with PHPT. The analysis included patients with PC ($n=74$), atypical adenomas (AA, $n=23$) and adenomas (A, $n=1540$). The demographic, clinical and laboratory features were compared between groups. Statistical analysis was performed with package Statistica 13 (StatSoft, USA) and SPSS (IBM, USA) and Bonferroni correction was used for multiple comparisons.
Results
PC was identified in 2,4% and AA in 0,8%. Most of the cases were reported in last 9 years of study ($n=52$). Age of PHPT manifestation in the PC group was 53 year [43; 62], in AA 61.5 [43; 72] and A 56 [48; 62] ($P=0.0092$). The ratio of men to women in PC was 1:4, AA 1:3.6, A 1:10 ($P=0,001$). Levels of intact parathyroid hormone (iPTH, 15–65 pg/ml) were significantly higher in PC compared to AA and A (1024 [356; 1772] vs572 [3544; 1569] vs 174 [115; 305.5] respectively, $P<0$, 001). Surprisingly the total calcium (Ca, 2.15–2.55 mmol/l) and ionized calcium levels (Ca+, 1.03–1.29 mmol/l) were higher in AA compared to PC and A: Ca 3.24 [3.01; 3.51] vs 3,18 [2.82; 3.6] vs 2.78 [2.63; 2.97], Ca+ 1.69 [1.59; 1.91] vs 1.55 [1.39; 1.69] vs 1.39 [1.29; 1.51], $P<0.001$). The most frequently localization of the PC was a right lower PG (32.4%). PC patients had more often bone fractures than AA and A (30% vs 22% vs 18% vs $P<0.001$). However, AA patients compared to PC and A had a higher frequency of osteoporosis (65% vs 62% vs 45%, $P<0.001$), nephrolithiasis (52% vs 43% vs 0.4%) and GFR reduction (48% vs 28% vs 9%, $P=0.002$). The prognostic significance for PC was excess of PTH more than 538 (sensitivity 80%, specificity 84%, AUC=0.866) and Ca more than 2.97 (sensitivity 67%, specificity 75%, AUC=0.713) according to ROC analysis. Recurrences of PC were reported in 16 cases (22%).
Conclusions
Our results demonstrate the increased incidence of PC in Russia. Malignant parathyroid tumors are associated with more severe clinical manifestations PHPT compared to A.

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AEP165

Primary hyperparathyroidism in multiple endocrine neoplasia type 1 (MEN-1) according to the online russian registry

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Objective
Primary hyperparathyroidism (PHPT) is one of the most frequently diagnosed endocrine disorders. The Russian Registry of PHPT is an on-line web-based database with the aim to estimate the prevalence and main features of disease. PHPT in Multiple Endocrine Neoplasia type 1 (MEN-1) is associated with polyglandular and early involvement of parathyroid glands.

Material and methods
The database from The Russian Registry of PHPT was used for retrospective analysis. We compared MEN-1 and sporadic PHPT cohorts regarding clinical and biochemical parameters, differences in preoperative features, operative strategies and outcome. Statistical analysis was performed with the STATISTICA 7 (DELL, USA), the significance levels in the range from critical to 0.05 were considered.
Results
Of a total 3010 patients from Registry, 128 patients meet the clinical and genetic criteria of MEN-1 and MEN-2A syndromes. Summary genetic testing was performed in 89 patients, mutations in MEN1 gene were verified in 60 patients (2%, 6/3010), inRET gene - in 2 (0.07%), in CDC73 gene - in 6 (0,2%). As expected, the PHPT manifestation in MEN-1 group was observed earlier 39,5 [26; 51] compared to sporadic disease 59 [53; 67] years ($P<0,001$), average duration of disease before diagnosis was 13.2 [9;13] vs 6 [3; 11] years respectively ($P<0.001$). The presence of 2 or more MEN-1-associated neoplasia's was determined in 42%. The most frequent components were pituitary adenoma (71.9%), pancreatic tumors (40.4%) and adrenal adenoma (38.6%), while isolated PHPT was diagnosed in 3% (2/60). We did not find any differences in the PTH, phosphorus and creatinine levels, but suddenly more severe hypercalcemia was observed in MEN-1 group (2.85 ± 0.26 mmol/l vs 2.74 ± 0.28, $P=0.011$), possibly due to delayed diagnosis. 68% of MEN-1 patients had symptomatic PHPT more often with bone manifestation (38.6%). Multiple parathyroid involvement on the time of primary diagnosis was found in 15 patients with MEN-1. Primary surgical treatment was performed in 42/57 patients with MEN-1, but only 55% of them underwent initially subtotal or total parathyroidectomy. We found a greater frequency of relapses compared to sporadic form ($P<0.0001$), reoperations for recurrent PHPT occurred in 35/57.
Conclusion
PHPT is the most common and earliest endocrinopathy in patients with MEN-1. According to the Russian registry, the average age of MEN-1 associated PHPT diagnosis is shifted by 10 years, and the symptomatic course with severe hypercalcemia is dominant. Thus indicates a late diagnosis and insufficient awareness on the PHPT diagnosis in the context of MEN-1.

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AEP166

Neural network algorithm to determine the optimal range of PTH level for patients with end-stage chronic kidney disease to maintain bone metabolism

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Secondary hyperparathyroidism is highly prevalent in patients with end-stage chronic kidney disease (CKD). Optimal range of PTH level for this cohort of patients is still controversial. The aim of the study was to use a neural network algorithm to determine the optimal point value and confidence interval for the average PTH value for patients with end-stage chronic kidney disease to maintain bone metabolism.
The study included 190 patients with end-stage CKD receiving renal replacement therapy. Blood levels of parathyroid hormone, total calcium (Ca), phosphorus (P), levels of markers of bone metabolism: alkaline phosphatase (ALP), osteocalcin (OK), C-terminal telopeptides of type I collagen (CTx) were evaluated in patients. Bone mineral density (BMD) was determined by double x-ray absorptiometry. For clustering patients into groups, a neural network algorithm (auto-encoder) was used, consisting of an encoder and a decoder. Four clusters were obtained, one of which determined optimal indicators of BMD status, markers of bone metabolism, and also the best patient survival. The optimal value of PTH in terms of supporting bone metabolism and better survival rates of dialysis patients is in the range of 114–490 pg/ml. The point estimate of the average PTH value is 234 pg/ml, the variance is 188 pg/ml. Both a decrease and an increase in PTH can lead to a critical imbalance in bone metabolism and an adverse outcome, including loss of BMD and shortened life expectancy. In addition to the level of PTH, an adaptive increase in osteocalcin and CTx, and an age-associated decrease in BMD are important in determining the prognosis of bone tissue and patient survival. These factors must be taken into account when diagnosing secondary hyperparathyroidism and determining the tactics of its treatment and observation.

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AEP167

The trabecular bone score predicts vertebral fragility fractures and decrease in volumetric bone mineral density in postmenopausal women

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Background
Osteoporosis frequently occurs in elderly people and is commonly associated with fall and fractures which leads the increase of morbidity and mortality. Therefore, precise prediction of osteoporotic fracture is important in clinical setting. The objective of this study was to investigate the association between baseline compression fracture and trabecular bone score (TBS) and was to assess the ability of TBS to predict vertebral fragility fracture and changes of volumetric BMD (vBMD) in postmenopausal women.
Materials and Methods
We enrolled 270 postmenopausal women aged over 46 who visited our hospital for a health check-up between Sep, 2013 and Sep 2017. TBS was calculated from dual energy X-ray absorptiometry and vBMD was generated from central quantitative computed tomography (cQCT). Both baseline and follow-up X-ray images were reviewed for the evaluation of thoracolumbar vertebral compression fracture which were defined according to the Genant criteria.
Result
At baseline, 76 (28.1 %) compression fractures were identified in 270 participants and the additional or progressive fractures occurred in 21 participants (7.8 %) for the median 19.5 month of the follow-up period. The median TBS was significantly higher in participants without vertebral fracture (median: 1.326, interquartile range [IQR]: 1.264 – 1.372) compared with that of those with vertebral fracture (median: 1.246, IQR: 0.169 – 1.308, $P<0.001$). During the follow-up, the deteriorated TBS value (≤ 1.31) were significantly associated with osteoporotic change of BMD assessed by cQCT using Kaplan-Meier analysis (Hazard ratio [HR]; 2.423, confidence interval [CI]: 1.708–3.438, $P<0.001$). Lower TBS (Hazard ratio [HR]; 2.505, confidence interval [CI]: 1.062– 5.911, $P=0.036$) was also revealed as a significant risk factor for the future vertebral fragility fracture.
Conclusion
The patients who had the deteriorated status of TBS showed more frequent predisposing compression fracture. In addition, it was suggested that TBS has the potential to predict future vertebral fractures in patients.

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AEP168

Inactivation of diabetoporosity-associated miRNAs in human mesenchymal stem cells

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Introduction
Osteoporosis is a disease characterized by the loss of bone density and deficits in bone microarchitecture. "Diabetoporosity" is a new term for osteoporosis in diabetes mellitus type 2 (T2DM) patients, where classical tools for the assessment of bone properties like dual x-ray absorptiometry or bone turnover markers are lacking prognostic accuracy for the determination of bone quality and fracture risk.
MicroRNAs (miRNAs) are getting into the focus of research not only for their importance in the development of osteogenic lineage cells, but also as biomarkers for bone related diseases. Sequencing of serum samples of elderly T2DM patients with prospective fractures identified differentially expressed miRNA compared to control serum samples. Here we have removed some of the identified microRNAs by CRISPR/Cas and examine the function of these microRNAs upon osteoblast differentiation of immortalized human mesenchymal stem cells (hMSC-TERTs).
Materials and methods
Serum samples of patients with T2DM who developed fractures within two years of follow-up were compared to serum of T2DM patients without

fractures. miRNA sequencing was performed in serum of 10 non-fracture and 6 fracture patients. Immortalized human bone marrow derived mesenchymal stem cells expressing Cas9 (MSC-TERT ^{Cas9}) were used to delete selected miRNAs. Guide RNAs were designed, cloned into the plasmid phU6 and transfected in MSC-TERT^{cas9} cells. Individual cells lacking miRNAs were clonally expanded.
Results
miRNA sequencing analysis of serum samples revealed 16 miRNAs (FDR < 0.05) that correlated with prospective fractures in elderly diabetic patients. miRNAs with average relative counts between 100 and 10000 were chosen for further analysis. 8 of the selected 9 were expressed in MSC-TERTs and considered for functional analyses and deletion. Successful creation of three microRNA deletion strains, namely miR140-KO, miR25/93/106b KO and miR-363/19b-KO, could be confirmed by PCR and sanger-sequencing.
Discussion
The establishment of cells lacking our target miRNAs is the first step for the examination of their importance during osteoblast differentiation of hMSCs. Further experiments will reveal the function of these miRNAs in the context of the differentiation potential of the created cell lines.

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AEP169

Fracture risk in patients with acute poliomyelitis§ going through late adulthood

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Objective
While osteoporotic fractures are reported in up to 40% of post-poliomyelitis adults, clinical guidelines regarding bone mineral density (BMD) testing and best timing for initiating treatment in this population are scarce. We assessed the characteristics of post-poliomyelitis patients, focusing on fracture and osteoporosis as the primary outcomes.
Methods
We conducted a cross-sectional retrospective data analysis from medical records of 204 post-poliomyelitis patients regarding their clinical characteristics, acute poliomyelitis disease and bone metabolism status.
Results
Our cohort included 53% females, mean age was 65 years (yrs.) at study entry and 1.7 yrs. at diagnosis of acute poliomyelitis. The lower limb was involved in 97.5% of patients, and the BMD in the affected limb was lower than the unaffected one (T score (Tsc) –1.64 vs –1.19, respectively; $P=0.06$). This difference was more evident in males than females (Tsc-1.85 vs –1.02, respectively; $P=0.07$), and in the fracture vs the non-fracture group (T-1.9 vs –1.25, respectively; $P=0.09$). Recurrent falls were documented in 39.2% of patients. Osteoporosis was diagnosed in 20.6% of patients and was more frequent in females ($P=0.003$) and patients with fractures ($P=0.002$). At least one fracture occurred in 52.2% of patients, and more than one in 40.3%, with a mean age of 57 yrs. at the first fracture. Most patients fractured their affected limb (73.1%).
Conclusion
Despite the high fracture risk, osteoporosis in late-adulthood post-poliomyelitis patients appears●to be underdiagnosed and undertreated. A comprehensive bone health assessment and early initiation of treatment, including anabolic agents, should be considered in this population.

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AEP170

Long term effect on trabecular bone score but not BMD is preserved in GH-deficient adults only when sufficient vitamin D levels are maintained

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Introduction
Adult growth hormone deficiency (AGHD) is associated with lower bone mass and likely with increased risk of fragility fractures. GH replacement leads to increase in bone mineral density (BMD) and trabecular bone score (TBS). The effect of adequate levels of vitamin D during GH replacement is important to provide effect on TBS.
Aim
To assess long–term effectof recombinant GH replacement on BMD and TBS with regards to vitamin D levels during period of 8 years.
Patients & Methods
Prospective follow-up of AGHD patients at one single center. Allpatients with adult GHD followed at single center. All participants were replaced with daily injection ofrecombinant human (rh) GH in IGF-1 normalizing regimen according to Endocrine Society Guidelines. From total number of 63 patients, 31 patients ended 8 years follow-up period with BMD measurement [at lumbar spine (L-spine) and total hip (TH)] and TBS performed at year 8. Deficiencies of other pituitary axes were treated if necessary. All patients were supplemented with 800 IU /day of cholecalciferol and 1000–1200 mg/day of calcium as recommended by International Osteoporosis Foundation. The study cohort was divided based on 25(OH)D levels into two groups with the cutoff defined as the median at each time-point of follow up.
Results
Study group consisted of 16 males and 15 females (14 with adult onset (AO) /17 with childhood onset (CO); mean age at diagnosis 25.03 yrs) AGHD patients. Average dose of rhGH was 0.4 mg/day and after six month of treatment IGF1 levels stayed in reference range (±2 SDs for age). After 8 years of GH replacement, increase of 8.7% and 8.2% (both $P<0.05$) for LS and TH BMD but not TBS was observed. TBS decrease of 2,2% in patients with 25(OH)D levels below median (24.1 mg/l) and slight increase +0,8% ($P=0.05$) in group with 25(OH)D levels above median was observed. BMD in both groups increased similarly.
Conclusion
Long-term GH replacement in adult GHD led to increase in BMD, but not TBS. However, after adjustment for vitamin D levels, patients with vitamin D below median showed significant decrease in TBS but no difference in BMD at both sites. In addition slight TBS increase was observed in patients with vitamin D above median. This study has shown that adequate vitamin D levels in GH-replaced have beneficial effect on bone quality, as measured by TBS.

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AEP171

Does real-life time spent within the therapeutic range affect degree of improvement in bone mineral density in men receiving testosterone therapy for hypogonadism?

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Background
Hypogonadism in males is associated with a reduction in bone mineral density (BMD). It is known that the reversal of this is achievable through adequate hormone replacement; however, the degree to which this is dependent on the proportion of time patients spend within the recommended therapeutic range (>15 nmol/l) in real-ife has not yet been established.
Aim
To evaluate the degree to which the proportion of time that a hypogonadal patient's testosterone levels are maintained within the target range affects the magnitude of their BMD improvement.
Methods
This retrospective, longitudinal observational, study included 115 patients aged 25–87 (±15.1) treated ata regional tertiary centre between 2006 and 2019. BMD measurements were performed using Bone Densitometry (DXA).The target range of testosterone >15 nmol/l was used as per nationalguidelines. Proportion of time spent within target range (TST) was expressed as a percentage of the treatment duration and grouped into 4 ranges; <25, 25–50, 50–75, >75%. Between-groups differences were analysed using the Kruskal-Wallis test.

Results
Mean percentage of treatment duration spent within target range was 44.2±27.2 with 43 (42%) of patients exhibiting an increase in *t*-score values for both Femoral Neck (FN) and L2-L4 measurements during their treatment period. The median change in bone mineral density for FN BMD was 0.2 and for L2-L4 it was 0.4. Median improvement in FN BMD for <25%=–0.05; 25–49%=0; 50–75%=0.1; >75%=0.2 showing a linear increase across groups, however differences lacked statistical significance ($P=0.64$). For L2-L4 BMD measurements, the median improvement values were <25%=–0.4; 25–49%=0.5; 50–75%=0.3; >75%=0.3. These scores between groups were also not statistically significant ($P=0.92$).
Conclusion
The results of this real-life longitudinal, retrospective observational study did not show a significant association between time spent in recommended target range of testosterone and an increase in BMD. Whilst a relationship is evident for the FN scores, the absence of a statistically significant difference potentially implies the influence of multiple confounders in practice. Cofounders, such as low sample numbers, should be explored and other modalities of bone protection should also be considered for BMD improvement in these patients.

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AEP172

Primary hyperparathyroidism diagnosis with 18-F-fluorodioline Pet/CT (FCPCT) in a routine endocrinology praxis: Need of the new guidelines

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Background
Primary hyperparathyroidism (pHPT) is a common disease in a routine endocrinology praxis, but the biggest challenge is a localization of the adenoma and the further correct management of the disease. First FCPCT was reported in 2014 as the additional method of diagnosis of pHPT and in some centers has been already used as a first line diagnostic modality. However, FCPCT is still lacking in the European or International guidelines for the diagnosis of pHPT.
Methods
Patients with biochemical and clinical pHPT between January 2017 and august 2019 were included in the study. Baselines characteristic, clinical data, scan results and type of treatment were recorded.
Results
A total 39 patients (32 F) were included in the study, mean age at diagnosis 57.6 ± 11.7 (31–81), 21 patients were asymptomatic 54%. Osteoporosis was diagnosed at 45% of 11 patients by DEXA. One patient had previously diagnosed multiply fractures. 17 patients 45 % had positive Sestamibi scintigraphy and/or echography and/or Dual-isotope 99mTc-MIBI/123 Iwere successfully operated. 22 patients with inconclusive echography, Sestamibi scintigraphy and Dual-isotope 99mTc-MIBI/123 I received FCPT, 18 (81%) were positive and 16 later operated with positive outcome (100% specificity). Two patients refused the operation. Four negative: two patient did not receive any treatment, two remaining are clinically controlled under Mimpara.
Conclusion
In our little retrospective study we showed high detection rate per patient of FCH PT scan (81%) with operation after positive scan and Mimpara treatment by negative patient. We conclude that FCHPT should be included in the diagnosis and the treatment choice of pHPT. Moreover, the current guidelines should be added FCPT as diagnostic possibility by inconclusive other modalities.

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AEP173

Quality of life, depressin and anxiety in patients with hypoparathyroidism

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Patients with hypoparathyroidism may have sypmptoms consistent with physical, emotional and cognitive dysfunctions which may cause impaired quality of life (QOL). We included 266 patients (20–79 years; 231 women/35 men) who were being treated for hypoparathyroidism. They were taking conventional therapies for hypoparathyroidism; calcium, active vitamin D and magnesium when needed. We applied Beck Depression Scale, Anxiety Scale and SF-36 QOL scale to the patients. The etiologic factors were thyroid surgery ($n=198$), autoimmune ($n=41$) and surgery for thyroid cancer ($n=27$). The etiologic cause of hypoprathyroidism did not show any correlation with questionnare scores. As thyroid cancer might be an additional stress factor we evaluated it as an independent factor but it had no impact on parameters. Duration of hypoparathyroidism had no effect on parameters ($P=0.662$). Serum calcium, and magnesium had a negative correlation with anxiety and depression scores (anxiety; $P=0/r=–0.336$, $P=0.001/r=–0.210$, depression; $P=0/r=–0.258$, $P=0.001/r=–0.210$, respectively). SF-36 parameters did not have any correlation with serum calcium and magnesium. Serum phosphorus and vitamin D levels did not have any correlation with depression, anxiety or SF-36 parameters. Frequency of admission to the emergency unit with hypocalcemic crisis did have a positive correlation with anxiety and depression scores ($P=0.001/r=0.202$; $P=0.004/ r=0.171$, respectively) and a negative correlation with general health status ($P=0.001/r=–207$). Compliance to the therapy (skipping calcium, magnesium or active vitamin D preparations) affected patients' scores. Anxiety and depression scores were higher among noncompliant patients (anxiety; 25.6±14.9 vs 18.6±12.7, $P=0$, depression; 18.4±12.7 vs 13.7±11.6, $P=0.001$, respectively). As expected SF-36 scores were lower among noncompliant patients (vitality; 39.1±21.6 vs 49.3±22.1, $P=0$, mental health; 54.1±18.7 vs 59.3±20.2, $P=0.027$, social function; 59.1±25.6 vs 67.5±25.4, $P=0.004$, bodily pain; 49.8±28 vs 56.9±27.7, $P=0.031$, general health; 43.2±20.9 vs 49.4±19.6, $P=0.012$). Conventional therapy does not meet the needs of patients with hypoparathyroidism. It has been shown thatnewly discovered parathyroid hormone therapy may improve QOL of patients. Further studies are needed.

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AEP174

Colour doppler ultrasound: Preoperative location of parathyroid adenomas in primary hyperparathyroidism

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Introduction
Parathyroid adenoma is the most frequent cause of primary hyperparathyroidism (PHPT). In recent years minimally invasive surgical techniques have challenged the traditional bilateral neck exploration. There are different imaging techniques for preoperative location of parathyroid adenomas. In this study the authors review the role of Doppler ultrasound focusing on its safety, availability and affordability.
Aim
To evaluate the role of Doppler ultrasound on preoperative location of parathyroid adenomas in patients with PHPT.
Methods
Retrospective study based on data from patients with PHPT that underwent parathyroidectomy between 2013 and 2019. Statistical analysis with Excel and IBM SPSS Statistics 20.
Results
Parathyroidectomy was performed in 135 patients (78,5% females) with PHPT between January 2013 and January 2019. The median age at diagnosis was 66 years old (22–89 years old). The median serum calcium and PTH were 11 mg/dl and 188 pg/ml respectively. The median follow up time was 2 years. Most patients performed 2 exams in order to detect the enlarged parathyroid(s). Cervical ultrasound without Doppler was the most performed exam (77%) and detected the lesion in 26% of the patients. The second most performed exam was sestamibi parathyroid scintigraphy (63.7%) and lesion was found in 62.8%. Doppler ultrasound was the third most requested exam (57.8%) and detected parathyroid adenoma in 88.5%. Parathyroid 4D computed tomography was performed in 37.8% of the patients and was diagnostic in 76.5%. In the group of patients that performed Doppler ultrasound ($n=78$), the median adenoma size was 18 mm (5–34 mm). Preoperative location of the parathyroid adenomas based on Doppler ultrasound was compared to the surgical and histological findings. 90.9% were accurately located on the superior poles and 63% on the inferior. 82.4% were correctly located on the right side of the neck and 88.2% on the left. Diagnosis accuracy was not affected by the presence of thyroid nodules ($P=0.728$). In 9 patients Doppler ultrasound did not find lesion and bilateral neck exploration was needed in 4 of them.
Conclusions
In this study Doppler ultrasound showed high diagnostic accuracy even in patients with nodular thyroid disease. Furthermore, its safety, affordability and availability should favor its use as a first line exam on preoperative location of parathyroid adenomas in PHPT.

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AEP175

Normocalcemic primary hyperparathyroidism in patients with elevated parathormone (PTH) in a regional health area. A laboratory based approach.

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Normocalcemic primary hyperparathyroidism (nPHPT) is still a poorly understood entity, characterized by increased circulating parathormone (PTH) and normal total and ionic calcium, excluding secondary causes.
Aim
To characterize the cases of nPHPT detected for a whole year from laboratory records of PTH in a tertiary referral centre, with the purpose of assessing a preliminary estimation and describing their main features.
Material and methods
Retrospective study of a database from the Biochemistry laboratory at "Marqués de Valdecilla" University Hospital (Santander, Spain) including the results of all PTH requests throughout 2018 coming from Primary Care and Hospital departments in Cantabrian health areas I-II (population 420,000).
Results
From 13,201 PTH determinations performed during 2018 in our lab, 4,746 showed an increased iPTH level (>65 pg/ml). Amongst them, 386 samples from 350 patients met the following criteria: normal corrected total calcium (8.1-10.4 mg/dl), normal renal function (eGFR >60 ml/min) and vitamin D sufficiency (>20 g/ml). Then, their electronic records were reviewed and secondary causes of hyperparathyroidism were excluded according to the 4th International Workshop guidelines. Eventually, 31 patients met the diagnostic criteria for nPHPT based on 2 normal values of corrected total calcium, but only 10 had a concomitant determination of ionic calcium, considered as mandatory to confirm nPHPT by the 4th International Workshop. At last, 6 of these 10 patients showed a normal ionic calcium level (1.18-1.30 mmol/l). Regarding the main clinical features of these 6 patients, 2 subjects had been diagnosed of osteopenia/osteoporosis, another one had had previous bone fractures and 3 of them urological findings (only one with confirmed renal lithiasis). In 2 of these 6 patients parathyroid scintigraphy was requested; in one of them a parathyroid adenoma was suggested.
Conclusions
Very few cases of nHPTP were found amongst PTH determinations performed upon suspicion in our health area, suggesting a low prevalence of this entity. Ionic calcium determination is still underused to confirm its diagnosis.

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AEP176

NGS sequencing proves as a powerful method to perform differential diagnosis in patients with inactivating PTH/PTHrP signaling disorders (iPPSD)

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The impairment of the parathyroid hormone (PTH) signaling pathway determines a group of related and highly heterogeneous disorders associated or not with the Albright's hereditary osteodystrophy (AHO) phenotype, classified as inactivating PTH/PTHrP signaling disorder (iPPSD). iPPSD features are rather difficult to be identified in some casesbecause manifestations are somewhat variable and some AHO characteristics are not specific to a specific disorder. Actually, besides *GNAS*defects causing pseudohypoparathyroidism (PHP), additional genes of the PTH pathway have been associated to other disorders, that should be considered for establishing a correct diagnosis in patients with no *GNAS* alterations. The aim of the present work was to discovermolecular alterations in iPPSD patients withno GNAS defects by NGS target sequencing and, afterreview of available clinical data, to identify manifestations useful for an early classification of patients. We investigated by NGS target sequencingof iPPSD associated genes (*GNAS*, *PRKAR1A*, *PDE4D*, *PDE3A*, *PTH1R*, *PTHLH*, *HDAC4*, *HOXD13* and *TRPS1*) 58 patients referred to our laboratory with a clinical diagnosis of iPPSD, in whom previous genetic testingfailed to identify any *GNAS* molecular defect. Deleterious variants were filtered and prioritized according toACMG/AMP pathogenicity scoresby the eVai v0.6 tooland potentially causative rare variants were confirmed by Sanger sequencing. By the bioinformatic analysis we discovered 5 novel highly damaging genetic variants, 3 in the *PTHLH* gene and 2 in the *TRPS1* gene, and, after re-evaluation of available clinical data, patients were re-diagnosed as suffering from brachydactyly with short stature (BDE2) and tricho-rhino-phalangeal syndrome (TRPS), respectively. All mutated patients presented both frequent and rare features commonly observed in PHP, BDE2 and TRPS. In particular, TRPS patients were mistakenly identified as PHP because they presented ultrarare signs, PTH resistance in one case and intellectual disability, obesity and subclinical hypothyroidism in the other one, that were already reported in the literature for single cases. In conclusion, our work allowed, by using a NGS gene panel for iPPSD-associated genes, to establish a correct genetic diagnosis, follow-up and genetic counseling in 5 patients misdiagnosed as PHP and to discover novel mutations in *PTHLH* and *TRPS1* genes. No genotype-phenotype correlations were observed and, unfortunately, we did not identify distinctive phenotypic features that could be exclusively associated to a specific syndrome different from PHP and could help in an early classification of patients.

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AEP177

Incidence of hypercalcemia and its causes in spain in a fifteen years period (2001–2015)

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Background and aims
Hypercalcemia is a rare ionic disorder and is often overlooked. The aim of this study was to describe the annual incidence of hypercalcemia in the adult population in Spain during a period of fifteen years, using the International Classification of Diseases, 9th Revision Clinical Modification (ICD-9). The diseases and procedures associated with this condition were also assessed.
Materials and methods
Data from the Minimum Basic Data Set of discharged patients older than 14 years old from the Spanish National Health System (Ministry of Health Affairs) between 2001 and 2015 were analyzed to describe the profile of patients with diagnostic codification of hypercalcemia (ICD-9: 275.42).
Results
41,075 unique patients were identified. The annual incidence is shown in Table 1. 22.3 % of the patients had no identifiable cause of hypercalcemia. 91 % of patients with known causes of hypercalcemia had one reported, 8 % had two, and 1 % had three or more. The most common identifiable causes were: neoplasia 87.8 %, hyperparathyroidism 15.3 %, thyrotoxicosis 2.1 %, parenteral nutrition 1.5 %, sarcoidosis 0.9 %, A-D vitamin poisoning 0.4 %, adrenal insufficiency 0.4 %, thiazide poisoning 0.3 %. Among the neoplastic causes, the most common were: lung cancer 19.8 %, multiple myeloma 14.7 %, breast cancer 6.9 %, gastrointestinal duct cancer 5.1 %, lymphoma 3.9 %, kidney cancer 3.7 %, bladder cancer 3.6 %, hepatobiliopancreatic cancer 3.6 %, prostate cancer 2.8 %. Among cancer patients, 50.6 % had metastatic spread: bone 53.5 %, liver 39 %, lung 27.4 %, serosa 15.1 %, central nervous system 9 %, other 46.7 %. Others conditions associated with hypercalcemia were: acute kidney failure 18.4 %, delirium 6.7 %, lithiasis 1.6 %, phosphorus disorders 0.9 %, magnesium disorders 0.9 %. In-hospital mortality was 26.9 %.

Year	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
×10,000 admissions	7	6.9	7	6.6	7.7	7.2	7	7.3	8.1	8.5	9.3	10.1	10.3	10.7	11.7
×100,000 inhabitants	5.9	5.8	6	5.7	6.5	6.1	6.1	6.3	6.9	7.3	7.9	8.5	8.7	9.2	10.1

Conclusions
The annual incidence of hypercalcemia among the admitted patients in the Spanish National Health System had a notable and constant increase between 2007 and 2015. The actual incidence is probably higher as this condition is underreported. The most common etiologies are neoplastic disorders, followed by hyperparathyroidism.

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AEP178

Management of severe hypercalcemia secondary to primary hyperparathyroidism: The efficiency of saline hydration, furosemide, and bisphosphonates.

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Introduction
Severe hypercalcemia is a life-threatening condition which should be managed urgently. Its pharmacological treatment consists of intravenous saline hydration, loop diuretic and intravenous administration of bisphosphonates. However, data evaluating these treatments are very limited.
The aim of this study was to assess the efficiency of saline hydration, furosemide, and bisphosphonates in the management of severe hypercalcemia secondary to a primary hyperparathyroidism (PHPT).
Methods
We conducted a retrospective analysis in 50 patients with severe hypercalcemia (≥120 mg/l) secondary to a PHPT. Clinical, biological and treatment data were collected regularly. The efficiency of each therapeutic agent was evaluated according to the variation of calcium levelcalculated as: □ calcium = Baseline calcium level –minimal calcium level after the administration of each agent.
Results
The study population included 41 women and 9 men with a mean age of 58.9 ± 12.9 years. At baseline, they had a mean serum calcium level of 133.2 ± 14.5 mg/l [extremes: 120–180] and a mean parathormone level of 682.4 ± 600.9 ng/l. Acute renal failure was diagnosed in 15 patients (30%). Thirty six patients received normal saline hydration alone with a mean duration of 5.9 ± 1.1 days with an infusion of 3-4 liters/24 h. The calcium level decreased to 120.1 ± 13.1 mg/l ($P < 10^{-3}$) with a □ calcium of 13.1 ± 14.5 mg/l. Normalization of calcium level occurred in only one patient (3%). Furosemide was prescribed in 36 patients with a mean dose of 60 mg/day [extremes: 20–120]. It resulted in a calcium decline of 12.1 ± 11.3 mg/l (before: 132.5 ± 15.1 mg/l, after: 120.4 ± 9.3 mg/l, $P < 10^{-3}$). Normalization of calcium level occurred in only one patient (3%). Twenty one patients received intravenous bisphosphonates. The mean maximal reduction in serum calcium level was 24.2 ± 8.9 mg/l [extremes: 6–44] reached 5.2 ± 3.2 days after the administration of bisphosphonates (before: 132.1 ± 8.8 mg/l, after: 107.85 ± 9.75 mg/l, $P < 10^{-3}$). Normalization of calcium level occurred in 8 patients (38%).
Serum creatinine level significantly decreased in all patients ($P < 10^{-3}$).
Conclusion
Our results demonstrated the absence of a significant additional effect of furosemide on calcium level in patient with severe hypercalcemia as compared to the effect of saline hydration alone. However, bisphosphonates were more potent. Thus, appropriate normal saline hydration and immediate intravenous bisphosphonates infusion should be considered in the pharmacological management of severe hypercalcemia in patients with PHPT.

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AEP179

Modeling to estimate the prevalence of chronic hypoparathyroidism in the absence of population-based studies

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Hypoparathyroidism is a rare endocrine disorder characterized by insufficient parathyroid hormone levels in the blood, low serum calcium and elevated serum phosphate. Studies evaluating the prevalence of chronic hypoparathyroidism (cHypoPT) are limited, and it is challenging to compare prevalence estimates owing tothe rarity of the disease and the difficulty of differentiating transient from permanent or cHypoPTin secondary data analyses. PublishedcHypoPTprevalence is between 9–37/100,000 from population-based studies in five countries. The objective of the study was to develop and evaluate two models that can estimate the prevalence of cHypoPTfor countries where population-based data are unavailable. We developed a thyroid surgery-derived model using data on thyroid cancer prevalence and probability of cHypoPT following thyroid surgery for countries where the relevant inputs were available from publishedliterature. We estimated the lifetime prevalence of thyroid cancer using historical cancer incidence data from cancer incidence registries and assumed most thyroid cancer cases undergo surgical resection. Using country-specific ratios of cancer-related versus non-cancer-related thyroid surgeries, we calculated lifetime prevalence of thyroid surgery. The proportions of thyroid surgeries leading to cHypoPT were applied to estimate the prevalence of surgical-related cHypoPT. Lastly, we summed up estimates of the prevalence of non-surgical and surgical-related cHypoPT. We considered gross domestic product (GDP) as a proxy for important risk factors for cHypoPT: healthcare quality and access, surgeon technique/skill, follow-up care and complication rates. We identified published population-based estimates for cHypoPTprevalence for five countries; the corresponding country-specific GDP data were collected from the World Bank. We evaluated the correlation between GDP and chronic hypoparathyroidism prevalence using R^2 and exponential coefficient values. We used this correlation to model country-specific prevalence and compared estimates from both models with published prevalence estimates. cHypoPTprevalence strongly correlated with GDP ($R^2 = 0.86$; $P < 0.001$). Prevalence estimates obtained from both modelswere comparable. For the United States, the thyroid surgery-derivedprevalence was 22.8 per 100,000, comparable to the prevalence of ~23.2 that was calculated from published population-based estimates and 20.6 for the GDP-based model. In the absence of population-based studies, thyroid surgery-derived and GDP-based

models can be used to estimate the prevalence of cHypoPT. These two methods yielded comparable US prevalence estimates and accurately predicted US prevalence as reported in the literature. Further validation is required, but preliminary data suggest that these models can be used to predict prevalence in countries without population-based studies.
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AEP180

Baseline characteristics from the observational paradighm registry of patients with chronic hypoparathyroidism

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PARADIGHM is an actively recruiting, prospective, observational registry (NCT01922440/EUPAS16927). The primary objective is to evaluate the safety and effectiveness of recombinant human parathyroid hormone, rhPTH(1-84), treatment in patients with chronic hypoparathyroidism under routine clinical care. The secondary objective is tocharacterize the clinical course of chronic hypoparathyroidism under conditions of routine clinical practice. At enrollment, registry inclusion criteria are patients having a hypoparathyroidism diagnosis >6 months and receiving conventional therapy (CT; eg, calcium supplements and active vitamin D), rhPTH(1-84) plus CT, or rhPTH(1-84). We present baseline characteristics of patients as of a June 30 2019 data cut. Baseline was defined as the value entered at the time of enrollment (Visit 1). Baseline symptom data exclude patients who initiated rhPTH(1-84) prior to enrollment ($n=68$) and are herein presented as two groups: those subsequently prescribed with rhPTH(1-84) after enrollment or those treated with CT. All data are summarized descriptively. Patient data from 64 centers in Europe and North America were analyzed. In the analysis population ($n=737$), 587 patients (79.6%) were female, 620 (84.1%) were white, and the mean (SD) age was 49.1 (16.45) years. The mean (SD) BMI was 19.3 (5.73) kg/m^{2}and 30.0 (7.72) kg/m^{2}in patients aged <18 ($n=25$) and ≥18 ($n=587$) years, respectively. The primary cause of hypoparathyroidism was thyroid surgery ($n=547$ [74.2%]; of these, 281 [60.0%] underwent surgery for thyroid cancer). Endocrinologists were the prescribing specialists for most patients ($n=660$ [89.6%]). Vitamin D and analogs were prescribed for 90.1% of patients (calcitriol, 74.2%, native vitamin D, 47.4%, alfacalcidol, 7.9%), calcium for 81.0% (calcium carbonate, 57.9%, calcium citrate, 27.1%), and thyroid hormones for 71.2% (levothyroxine, 73.4%; liothyronine, 5.8%). Symptoms reported at enrollment for the rhPTH (1-84) ($n=66$) and the CT groups ($n=603$), respectively, included fatigue (53.0%, 39.3%), paresthesia (48.5%, 29.2%), muscle twitching (48.5%, 21.1%), muscle cramping (40.9%, 33.0%), headaches (33.3%, 17.6%), anxiety (28.8%, 20.1%), muscle pain (28.8%, 19.2%), tetany (28.8%, 12.1%), and brain fog (27.3%, 16.3%). The baseline data for the overall population appear to be representative of patients with chronic hypoparathyroidism. Baseline data suggest that at enrollment patients prescribed rhPTH(1-84) after enrollment appear to have an increased burden of disease than patients receiving CT based on symptoms. PARADIGHM will be a valuable resource of real-world longitudinal data for patients with chronic hypoparathyroidism.
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AEP181

Clinical presentations of patients receiving PTH-therapy among the referral population with hypoparathyroidism.

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This study aims to evaluate patients who require PTH-treatment among the referral population with hypoparathyroidism.
Methods
The information was collected from the registry database of chronic hypoparathyroidism, which was initiated by the National Medical Research Centre for Endocrinology (NMRCE).
Results
Among 194 cases of hypoparathyroidism referred to our clinic over 2 years (2017–2019), eight patients required PTH replacement treatment and six patients (3,09%) received treatment with teriparatide due to complete resistance to conventional therapy with alfacalcidol and calcium supplementation. The mean age of these 6 patients at evaluation was 52 ± 12 s.d. years (minimum 31 and maximum 71 years); the female-to-male ratio was 5:1. In 4 cases the subjects had postsurgical hypoparathyroidism (in 3 cases after thyroid surgery ($n=2$ thyroid cancer and $n=1$ thyroid goiter) and in 1 case after parathyroid surgery). Additionally 1 patient had autoimmune polyglandular syndrome and one male patient suffered from idiopathic hypoparathyroidism. In 3 cases of postsurgical hypoparathyroidism patients suffered from osteoporosis diagnosed before thyroid or parathyroid surgery. The longest duration of teriparatide treatment was 5 years at a dose of 20–60 mg/day with periodically used pump therapy. Treatment with teriparatide was cancelled after achieving remission of candidiasis which led to improved gastrointestinal absorption. Other patients continued treatment with teriparatide. The next longest treatment duration was three years at a dose of 40 mg in a patient with gastric resection due to ulceration; 2.5 years at a dose of 20 mg in a patient with colon pseudomelanosis; one subject received 40 mg over 12 months and two patients only started treatment with teriparatide at a dose of 20 mg over 6 and 7 months. The daily dose of calcium and active vitamin D were reduced and calcium levels within the reference range were achieved in all subjects. Serum phosphate was decreased in 3 subjects out of 6. Bone mineral density (BMD) was increased in all patients with osteoporosis.
Conclusion
Severe malabsorption is the most frequent requirement of PTH treatment. Teriparatide was effective in all subjects to alleviate symptoms and to achieve calcium levels within the reference range.
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AEP182

Clinical characteristics of subjects with very high serum 25 OH vitamin D levels in turkey: DeVIT-TOX survey

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Background
Treatment of vitamin D deficiency orinappropriate vitamin D supplementation may cause side effects associated with hypercalcemia. We observed a tendency to use very high single dose cholecalciferol for treatment of vitamin D deficiency.
Aim
The primary aim of this study was to examine the clinical characteristics of patientswith very high serum 25OHD levels of vitamin D toxicity in Turkey.
Materials and methods
An invitation was sent to all tertiary endocrinology clinics of Turkey to complete a retrospective survey for the diagnosed high serum 25OHDlevels (>88 ng/dl) and/or vitamin D toxicity, between January 2019 and December 2019. Twenty-threecenters responded from 19 cities. Subjects evaluated according to the presence of signs and or symptoms of hypercalcemia. The evaluation also is doneaccording to 25OHD levels >150 ng/dl (Group 1), 149–100 ng/dl (Group 2), 99-88 ng/dl (Group 3).
Results
Two hundred and fifty-three patients included in the final analysis (female/male: 215/38,: 51.5±15 yrs). Serum 25OHD level:119.9±33 (min-max 88-259) ng/dl, and serumcalcium level was 9.8±0.7 (min-max 8.1–13.1) mg/dl. Most ofthe patients were asymptomatic ($n=201$, 75.4%)despite high vitamin D and calcium levels. Serum 25OHD levels was significantly higher in the symptomatic group(138.6±64 ng/dl) compared to asymptomatic group (117.7±31 ng/dl) ($P<0.05$). Serum calcium levels were10.36±1.0 mg/dl vs 9.7±0.6 mg/dl ($P<0.01$) for symptomaticand asymptomatic groups, respectively. The symptomatic group was older than others ($P<0.05$). Serum intact PTH level was similar between groups. There was no significant difference in terms of age,serum calcium and iPTH levels in group 1,2 and 3. Inappropriate prescribed high dose oral vitamin intake (600.000-1.500.000 IU) in short term (1–3 months) for treatment ofdeficiency/insufficiencyis to the most common reason (73%) associated with high serum 25OHD levels.75.9% of patients who developed toxicity(serum 25OHD >150 ng/dl) used the vial form (300.000 IU/1 vial=1 ml) twice consequently.
Conclusions
High serum 25OHD levels were associated with very high dose vitamin D intake. To avoid vitamin D toxicity and related complications need to avoidusing very high dose of cholecalciferol. Clinical guidelines recommendations for the treatment of vitamin D deficiency are effective and safe.
Keywords: vitamin D, toxicity, hypercalcemia

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AEP183

The bone density and trabecular bone score in patients after solid organ transplantation

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Introduction
Organ transplant recipients are at increased fracture risk compared to general population. Bone mineral density (BMD), predictive of fracture in general population, does not reflect impaired bone quality frequently present in patients with advanced organ failure. Trabecular bone score (TBS) provides surrogate measures of bone microarchitecture and therefore helps to identify persons at risk for fracture among transplant recipients.
Methods
Our retrospective study comprises 186 persons (115 M, 71 W, age 54.4±12.0 y), 34 simultaneous pancreas and kidney (SPK) recipients, 60 kidney and 92 liver recipients, transplanted in 2018. Dual energy X-ray absorptiometry scans (DXA) and TBS measurement were performed with the Lunar Prodigy apparatus within the year of transplantation (Tx). Standard TBS was calculated from DXA images of the lumbar spine.
Results
Osteoporosis of L-spine (T score ≤–2.5) was present in 29/186 persons (16%), osteopenia (T score>–2.5 <–1.0) in 58/186 (31%). Proximal femur osteoporosis was diagnosed in 24/186 (13%), and osteopenia in 71/186 (38%) patients. Mean T score of spine was –0.9±1.5 and T score of hips –1.02±1.2. The lowest values of L spine T score among all were found in liver graft recipients mean-1.2±1.5 vs SPK recipients –0.7±1 ($P<0.05$) and for kidney recipients –0.5±1.7 ($P<0.05$). SPK recipient had the lowest T score of hips –1.7±1 vs the kidney Tx group (T score –1.0±1.3) ($P<0.01$) and for liver graft recipients (T score –0.8±1.2) ($P<0.001$). The total group TBS was decreased (mean 1.18±0.1) which corresponds to high risk values <1.23. The worst TBS was found in liver Tx patients 1.13±0.2, which differs significantly from SPK recipients cohort TBS 1.26±0.1 ($P<0.001$) and kidney recipients TBS 1.22±0.1 ($P<0.001$).
Summary
Bone density of L spine was decreased in 48% and proximal femur in 51% in patients after solid organ transplantation. The low TBS values in comparison with relatively preserved T score point to more prevalent bone microstructure damage present in transplant recipients.

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AEP184

Free 25-hydroxyvitamin D, but not free 1.25-dihydroxyvitamin D, predicts all-cause mortality in ageing men

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Background
Total 25 hydroxyvitamin D (25(OH)D) and total 1.25 dihydroxyvitamin D ($1.25(OH)_2D$) are associated with all-cause mortality. The free hormone hypothesis postulates that only the free vitamin D fraction can exert its biological function. Recently some studies suggested that free 25(OH)D levels might be a better predictor for clinical outcomes, including mortality.
Objective
To study the association between total and free 25(OH)D and $1.25(OH)_2D$ with all-cause mortality in a prospective cohort of community-dwelling European men.
Methods
1970 community-dwelling men, aged 40–79, participated in the European Male Ageing Study (EMAS) between 2003–2005. In 5 of 8 EMAS centres, survival status was available until 1 April 2018. Total 25(OH)D levels were measured by radioimmunoassay and recalibrated to NIST standard reference material. Total 1 $25(OH)_2D$ was measured by mass spectrometry and vitamin D binding protein (DBP) by immunodiffusion. Free 25(OH)D and free $1.25(OH)_2D$ were calculated from the total hormone and DBP concentration. Vitamin D measurements and DBP were divided into quintiles. Cox proportional hazard models were used to study the association between

vitamin D status and all-cause mortality. Because of the wide age range at inclusion, age was used as time scale instead of years since inclusion adjusting for age. Results were expressed as hazard ratios (HR) with 95% confidence intervals, adjusted for centre, BMI, smoking and self-reported health.
Results
524 (26.6%) men died during a mean follow-up of 12.3±3.4 years. Men who died had a higher BMI ($P=0.002$) and lower physical activity level ($P<0001$), but there was no difference in smoking status. Men in the lowest total 25(OH)D and the lowest total $1.25(OH)_2D$ quintile (cutoff <9.3 µg/l and <46 ng/l respectively) had increased mortality risk (HR compared to men in the highest quintile (HR 1.83 (95% CI 1.34–2.50); $P<0.001$ and 1.41 (1.04–.90); $P<0.05$ respectively). Likewise, men in the lowest three free 25(OH)D quintiles (levels <4.43 ng/l) had a higher mortality risk compared to men in the highest quintile (HR 1.91 (1.34–2.73); $P<0.001$ for the lowest quintile). However, mortality risk was similar for across all free $1.25(OH)_2D$ and DBP quintiles.
Conclusions
Low total 25(OH)D levels and low total $1.25(OH)_2D$ levels in community-dwelling middle-aged and elderly men have an increased future mortality risk. However, only low free 25(OH)D but not free $1.25(OH)_2D$ levels predict all-cause mortality. Vitamin D deficiency is associated with a negative impact on general health and is predictive of a higher mortality risk.

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AEP185

Calcium-sensing receptor gene polymorphisms and their effect on response to cinacalcet treatment in patients with secondary hyperparathyroidism in chronic kidney diseases

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Background
Secondary hyperparathyroidism (SHPT) is an adaptive process that develops in response to declining kidney function, impaired phosphate excretion, and failure to bioactivate vitamin D. The signal transduction via the calcium-sensing receptor (CaSR) is a key determinant of parathyroid gland hyperplasia.
Aims
To examine the polymorphisms rs1801725 (p.Ala986Ser, G>T), rs1042636 (p.Arg990Gly, A>G), rs1801726 (p.Glu1021Gln, G>C) of *CaSR* gene as a possible cause of the different responses to cinacalcet.
Materials and methods
In study were enrolled 25 patients undego chronic hemodialysis with SHPT (parathyroid hormone (PTH) levels greater than 800 pg/ml). The mean age of patients was 47 (21–77) years old. Patients were genotyped for rs1801725, rs1042636, rs1801726 of *CaSR* gene by Sanger sequencing. The initial dosage of cinacalcet was 30 mg/day. All patients were also tested for calcium-phosphate metabolism parameters.
Results
The baseline levels of albumin-corrected calcium were significantly lower in patients with polymorphisms rs1801725, rs1042636, rs1801726 of *CaSR* gene compared to the patients with wild type genotype ($P=0,01$). In 3 months cinacalcet treatment patients homozygous and heterozygous for the rs1801725 polymorphism did not demonstrate significant reduction in PTH from baselinecompared to the patients without this polymorphism in the genotype. The same situation was found for rs1801726 polymorphism carriers. The heterozygous patients for the rs1801726 polymorphismshowed-significant reduction in PTH andcalcium * phosphate product (Ca*P), while patients without this polymorphismshowed reduction in PTH,ionized calcium, albumin-corrected calcium,phosphate and Ca*Pfrom baseline. After 3 months treatment the homozygous and heterozygous patients for the rs1042636 showed significant reduction of PTH levels, while the patients without this polymorphism showed reduction in PTH, ionized calcium, albumin-corrected calcium, phosphate and Ca*P.
Conclusions
This study shows that polymorphisms rs1801725, rs1042636, rs1801726 of *CaSR* geneinfluence the effectiveness of cinacalcet treatment. The patients without this polymorphism showed a significantly higher sensitivity to cinacalcet compared to the patients who were carriers of *CaSR* polymorphisms.

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AEP186

An extremely rare cause of severe primary hyperparathyroidism due to intrathyroidal parathyroid cyst.

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Introduction
Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia, most cases with parathyroid adenoma as the underlying pathology. However, when blood and urine calcium levels and PTH are higher than normal in PHPT, t's important to suspect an ectopic PTH secretion or a parathyroid carcinoma. Intrathyroidal parathyroid cysts are extremely rare cause of severe PHPT.
Clinical case
A 36-year-old male presented with dizziness and weakness for several weeks. Osmotic polyuria and nocturia with thirst were also impairing his quality of life. He had no history of renal lithiasis or hypertension. Biochemical features were suggestive of PHPT (Ca^2:12.9 mg/dl; iPTH:>300 pg/ml; $Ca_{u:}$11.5mg/kg/24 h). Physical exploration shows normal thyroid palpation and there were no lipomas or facial angiofibromas. BMD was reduced and skull X-ray revealed a brown tumor. US also showed bilateral renal microlithiasis. No family background of MEN 1. CT showed a right thyroid nodule and a possible left parathyroid adenoma but Tc99m sestamibi scintigraphy revealed radio tracer uptake in the right lobe of thyroid. In ultrasonography no parathyroid lesions were located, but a solid-cystic nodule in the right lobe was observed. US-FNA of the thyroid nodule followed by cyst iPTH measurement (2,170,000 pg/ml) confirmed intrathyroidal parathyroid gland. Treatment with 30 mg of cinacalcet was initiated, but without calcium decrease until 210 mg daily dose. After sharing our clinical suspicion with the surgeon, an hemithyroidectomy was performed, checking that PTH dropped to normal levels. Twenty-four hours after surgery, the patient started with paresthesias and positive Trousseau sign, PTH level was of 5 pg/ml with normocalcemia. After resolution of symptoms with IV calcium, oral calcitriol and calcium carbonated were initiated. Two weeks after surgery both medications were stopped without symptoms at all.

Biochemical parameter	Baseline	Cinacalcet 120 mg	Cinacalcet 210 mg	24 hours after surgery	2 months after surgery (without treatment)
Albumin corrected calcium (mg/dl)	12,2	12,2	11,4	10,7	9,8
Phosphorus (mg/dl)	1,8	2,4	2,8	3,1	3,6
PTH(pg/ml)	258	257	332	5,7	20
25OH VitaminD (ng/ml)	42	16,8	18	×	20
Urine calcium (mg/kg/24 h)	11	7,5	4,3 (incomplete)	7,2	4,4
Glomerular filtration (ml/min/1.73m^2)	115	110	110	110	110

Conclusions
1. Intrathyroidal parathyroid cystic adenoma is an extremely rare cause of PHPT.
2. FNA-iPTH is a helpful tool to make an accurate diagnosis when an intrathyroidal parathyroid adenoma is suspected.
3. Elevated levels of PTH and bone disease before parathyroidectomy, are risk factors for hungry bone syndrome.

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AEP187

Skeletal manifestations of hypoparathyroidism mimicking ankylosing spondylitis; a rare clinical presentation: A case report

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Introduction
Idiopathic hypoparathyroidism is a rare endocrine disorder with varying clinical manifestations ranging from acute hypocalcemic symptoms to asymptomatic soft and skeletal tissue calcifications/ossifications. Patients may present with wide spectrum of rheumatological manifestations, which are under-recognized, thus delaying timely treatment. This results in chronic disability.
Case presentation
A 47-year-old male with past history of convulsions and non-specific musculoskeletal symptoms presented with chronic backache for 10-years duration, with clinical findings of spinal stiffness and kyphosis suggestive of ankylosing spondylitis. He was initially managed with non-steroidal anti-inflammatory drugs and disease modifying anti-rheumatoid drugs with poor response. He was also treated with sodium valproate for adult onset seizure disorder. Further, he had intermittent numbness of hands and positive Trousseau's and Chvostek's signs. Radiological evaluation revealed multiple anterior osteophytes in the spine, mainly in the lumbar region and prominent end plates with shiny corners. Left iliolumbar ligament was calcified with sclerotic changes in the left sacro-iliac joint and joint space reduction mimicking spondyloarthropathy. However, HLA B27 was negative. He also had bilateral cerebral, cerebellar and basal ganglia calcification on non-contrast computed tomography of head. Biochemical evaluation confirmed hypocalcemia secondary to hypoparathyroidism. Following treatment with calcium and vitamin D, patients' symptoms improved but skeletal changes mimiking spondyloarthropathy remained unchanged.
Conclusion
Long standing untreated hypoparathyroidism may lead to ligamental/joint ossification and calcifications resulting in spinal stiffness mimicking ankylosing spondylosis-like clinical picture. It is important to consider hypoparathyroidism as a differential diagnosis in the background of atypical spondyloarthropathies to avoid delay in diagnosis and to prevent chronic disability.

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AEP188

Hypercalcemia and primary hyperparathyroidism case progressing during the treatment of dapagliflozin

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Introduction
Hypercalcemia associated with the use of a SGLT-2 inhibitor is a very rare adverse effect. Herein we reported a case of apparent primary hyperparathyroidism that occurred while applying the treatment of dapagliflozin in a patient with asymptomatic primary hyperparathyroidism.
Case report
A 49-year-old male patient with 5 years of diabetes mellitus history admitted for his routine control and Hba1c level was observed 7.9%. Dapagliflozin (1 × 10 mg) was started to the patient who has been using metformin (2 × 1000 mg) and gliclazide (1 × mg). At 6 months of dapagliflozin therapy, calcium level was detected 11.28 mg/dl, creatinine level was 1.21 mg/dl, and phosphorus level was 3.73 mg/dl, parathormone level was 70.8 ng/l, 25-(OH) vitamin D level was 33.16 ng/ml. A 4 × 9 × 14 mm-sized hypoechoic lesion located inferior to the right thyroid lobe, which was compatible with a parathyroid adenoma was detected on the neck ultrasonography. Because 99m-MIBI scintigraphy does not show an uptake compatible with parathyroid adenoma, four-dimensional computed tomography and magnetic resonance imaging were performed to clarify the localization of parathyroid adenoma. A 15 × 10 × 9-mm nodular lesion, which was compatible with the parathyroid adenoma was observed adjacent to lower part of the right thyroid gland. A 24-hours urine calcium level was 492 mg/day. The patient underwent lower right parathyroidectomy. Histopathological findings confirmed the diagnosis of parathyroid adenoma. After three months of the surgery, the patient is still asymptomatic and followed up with normal calcium levels.
Conclusion
Thiazide use and excessive calcium intake have been previously reported in the in the development of hypercalcemia while using SGLT-2 inhibitors. In response to increased absorption of phosphorus from the kidney, FGF-23 and parathormone levels increase. Another reason why SGLT-2 inhibitors cause moderate increase in calcium levels is the inhibition of both SGLT-1 and SGLT-2 receptors and the increase in calcium absorption in the intestines. Volume depletion caused by SGLT-2 inhibitors may also contribute to hypercalcemia. As the result of these mechanisms, calcium level may be seen increased with the use of SGLT-2 inhibitors. SGLT-2 inhibitors are medicines which lead to hypercalcemia and to reveal parathyroid adenoma that is not symptomatic. İt should be considered that calcium following-up might be needed while using SGLT-2 inhibitors.

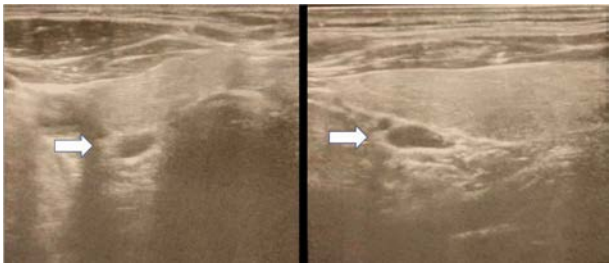

Figure 1 Ultrasonographic appearance of the parathyroid adenoma.

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AEP189

Radioiodine, hyperparathyroidism and schwannoma... coincidence or consequence?

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Background
Primary hyperparathyroidism (PHPTH) refers to overproduction of PTH (parathyroid hormone) which leads to hypercalcaemia and hypophosphataemia. Preoperative imaging aims identification of a solitary parathyroid adenoma (PTA) or multiple gland hyperplasia. However, it is not always possible to identify the lesions, and in some situations imaging findings could be misleading.
Case report
A 48-year old male, with personal history of differentiated thyroid cancer in 1998 (at age 27), underwent total thyroidectomy and multiple radioactive iodine (RAI) treatments (cumulative dose 610 mCi). During follow-up, there was no evidence of recurrent disease. He was lost for follow-up for several years.
In August 2018, he presented with signs and symptoms of hypercalcaemia, and was diagnosed with primary hyperparathyroidism (PHPTH). The neck ultrasound revealed a 3-cm hypoechoic heterogeneous mass in the left suprasternal region, suggestive of PTA. In April 2019, he underwent a resection of the mass with lateral neck lymph node dissection, the pathology report described the 3–cm mass as schwannoma, all other lesions resected as reactive lymphadenopathy. Postoperatively, he had persistent PHPTH. In May 2019, a 99mTc-Sestamibi scintigraphy with SPECT-CT identified two lesions with high uptake: one in the sternocleidomastoid muscle, with uptake on early imaging (10 minutes), with almost complete washout on late imaging (3 hours); and the other one in the right upper thyroid bed, with persistent uptake on late imaging. These lesions were excised, and the former one was reported as a reactive lymphadenopathy, while the latter one was confirmed as a PTA. Postoperatively, PTH levels immediately dropped from 267 pg/ml to 50.1 pg/ml. However, during follow-up, we identified persistently high PTH and Ca levels (92.9 pg/ml and 12.8 mg/dl in Jul 2019, 76.5 pg/ml and 11.7 mg/dl in Jan 2020). He repeated scintigraphy in Jan 2020, with no unusual uptake identified.

Discussion
Our case emphasises the importance of scintigraphy for differential diagnosis in PHPTH, even if the neck ultrasound identifies a suspicious lesion. Both schwannoma and lymphadenopathy could have a high uptake on scintigraphy, however the washout pattern is different compared to PTA. On the other hand, it reminds of higher incidence of PHPTH in patients treated with RAI, previously reported in literature. Also, hyperparathyroidism was reported as a possible aetiological factor of schwannoma. Hence, we could hypothesise that the lesions identified in our patient represent a linked sequence of events rather than a simple coincidence, with RAI for thyroid carcinoma causing hyperparathyroidism, and the latter contributing to development of schwannoma.

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AEP190

Multiple endocrinopathies associated with myotonic dystrophy type 1 – case report

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Introduction
Myotonic dystrophy type 1 (DMT1) is the most prevalent muscular dystrophy that affects 1 in 8000 individuals. Disease is caused by CTG repeat expansion of the DMPK gene located on chromosome 19. Beside neuromuscular involvement, studies have found an increased prevalence of endocrinopathies such as diabetes, hyperparathyroidism and hypogonadism. The exact underlying mechanism of endocrine dysfunction remains unclear. Moreover, endocrine dysfunction is progressive in nature as is the muscle affection. We illustrate the problem with following clinical case.
Case report
47-year old women, complaining of chronic fatigue, muscle weakness and anxiety was admitted to our department for an evaluation of low TSH, T4, T3, hypercalcemia, hypophosphatemia, and elevated PTH level. We performed pituitary MRI, neck ultrasound, ^{99m}Tc sestamibi SPECT/CT and all results were unremarkable. Other pituitary hormone testing showed normal findings. We diagnosed patient with secondary hypothyroidism and primary hyperparathyroidism, introduced levothyroxine along with hidration and furosemide and decided to do regular check-ups. However, patient was not feeling better with therapy. In the meantime, she underwent genetic testing for myotonic dystrophy type 1 as her son was diagnosed with severe form of disease after suffering cardiorespiratory insufficiency during influenza. Later on, her son developed primary adrenal insufficiency and primary hypogonadism. In further monitoring, our patient´s calcium and PTH levels where persistently elevated. Given the inability to locate hyperactive parathyroid tissue and an increased perioperative risk due to neurological disease itself, we decided to treat patient conservatively rather than surgically. Despite hidration, furosemide, pamidronate and cinecalcet, calcium levels did not decrease.^{18}F choline PET/CT is not a routine diagnostic method for this indication in our country. We performed it for the first time in this patient and found 6 mm large hyperactive tissue in the projection of the left lobe of the thyroid gland. Patient underwent surgery and finally calcium, phosphorus and PTH levels normalized. Couple of years later we noticed elevation in fasting glucose and HbA1c levels, so we started metformin therapy. She is well now but we keep monitoring the rest of the endocrine function, especially adrenal function.
Conclusion
Myotonic dystrophy type 1 and associated endocrinopathies are one more proof of neuroendocrine connection. In all patients suffering from it, endocrine evaluation and monitoring is obligatory. Although Consensus-based Recommendations from Myotonic Dystrophy Fundation do not mention screening of the parathyroid gland function, it is one of the most common endocrinopathy and should be evaluated in these patients as well.

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AEP191

Remission of disseminated parathyroid cancer after multiple surgical interventions because of recurrences in the neck lymph nodes, left lung and liver in a young patient with hyperparathyroidism-jaw tumor syndrome

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Background
Parathyroid cancer (PC) is a rare tumor associated with poor prognosis particularly when disseminated. Currently, the only effective treatment is a surgical intervention.
Case
Starting from the age of 19 a woman had been suffering from bone pains and change in gait. A low-energy right humerus fracture with displacement occurred when she was 23. At the same time, primary hyperparathyroidism (PHPT) was diagnosed for the first time (PTH 569 pg/ml (15–65), Ca total – 3.30 mmol/l (2.15–2.55)) and the right lower parathyroid gland (PG) was removed that led to a remission of the diseases. Histological examination showed PC. The first recurrence of PC with metastases in the neck lymph nodes developed in a year. The subtotal resection of the thyroid gland, a removal of pre- and paratracheal tissue, nerve-sparing lymphadenectomy on the right of the neck was performed with achievement of a remission of PHPT (PTH 4 pg/ml, Ca total 1.82 mmol/l). After 3 years (at the age of 29), there was a second recurrence of PC (Ca total 4 mmol/l, PTH 2 186 pg/ml) with metastases in S3 of the left lung (17 mm) and in the liver SII-III (17 × 17mm and 24 × 2.7 mm). A resection of the upper lobe of the left lung and liver resection (bisegmentectomy II -III with resection of the IV) was successfully performed in two stages. The metastases of PC verified by histological analysis and immunohistochemistry (IHC) of the removed distant lesions. The remission of the disease has been observed for the last two years (PTH 6 pg/ml, Ca total 2.08 mmol/l). Considering that the manifestation of the PHPT began at an early age and mothers' PHPT (parathyroid adenoma) a hereditary form of PHPT was suspected. Next-generation sequencing identified a germline mutation in the *CDC73* (c.355C>T:p.Q119X).
Conclusion
Patient with PC associated with a germline mutation in the *CDC73* has a poorer disease prognosis. In some cases, it is possible to achieve a remission of the disease by a surgical removal of distant metastases, but future studies must focus on searching a new effective treatment option.

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AEP192

Sequencing of the gnas gene in hungarian patients with pseudohypoparathyroidism and mccune-albright syndrome

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Introduction
The human GNAS gene is coding for the alpha stimulatory subunit of the guanine nucleotide-binding protein. This G protein stimulates the activity of the adenylate cyclase enzyme which is in control of the production of various hormones in endocrine glands and also regulates bone development. Mutations in GNAS can lead to McCune Albright syndrome, progressive osseous heteroplasia or pseudohypoparathyroidism.
Aim
Our aim was to find the genetic background of the disease.
Materials and methods
In this study we screened 24 people, 20 index patients and 4 relatives, 9 with preliminary McCune Albright indication and 11 with pseudohypoparathyroidism. For genetic testing peripherial blood was collected. In two cases tumor tissue samples were also available. Genomic DNA was isolated with Qiagen DNAeasy Blood and Tissue kit. PCR products were directly Sanger sequenced. Sequence data obtained were compared to NCBI and ENSEMBL databases.
Results
Out of 9 samples only one tissue (11%) tested positive for somatic mosaic (level 25–30%) mutation, p.MET703_ARG704del, thus for McCune Albright syndrome. In the case of pseudohypoparathyreosis 6 germ line mutations out of 11 index patients could be detected (54%). Inheritance of the mutations within families could be observed. In our samples one GNAS

c.2277delC frameshift mutation was found in heterozygotic form possibly causing truncated protein. The heterozygous Leu706Pro probably damaging (Polyphen2 score 1.0) variant, was found in the index patient but absent in the parents, likely originated de novo. The GNAS Arg231Cys known pathogenic mutation was found in three cases, one mother and two siblings. The c.432+1G>A splice mutation could be detected in one index patien and her mother, The known pathogenic heterogeneous 4 bp deletion rs587776829 was also detected.
Discussion
Six different mutations in 6 index patients (54%) were found and symptomes could be matched to pseudohypoparathyreosis type 1a. McCune Albright syndrome found in one case only shows the importance of testing somatic DNA samples is of critical importance here.
Acknowledgements
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AEP193

Mineral density of bone tissue, parathyroid hormone and vitamin D in children and adolescents with thyrotoxicosis
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Thyroid hormones have an important role in bone metabolism. In this case, hyperthyroidism causes secondary osteoporosis and osteopenia. There is very little information in the literature about the state of bone metabolism in children and adolescents with thyrotoxicosis. Thus, our work aimed to study the state of bone mineral density and levels of calciotropic hormones in children and adolescents with thyrotoxicosis. The study was conducted in a group of 19 children and adolescents with thyrotoxicosis at the age of 9–18 years. The control group consisted of 23 healthy children and adolescents. All studies were conducted in the RSSPMCE. Levels of TSH, fT4 and fT3, PTH and vitamin D were determined using a closed-type immunochemistry analyser Cobas e 411 Hitachi company HoffmanLeRoche (Switzerland) and its reagents. Bone mineral density was evaluated by dual-energy absorptiometry on a Stratos X-ray densitometer from DMS, France. The results of the study showed that the average value of the level of vitamin D in the control group was 20.4±6.2 ng/ml, in the group with thyrotoxicosis – 12.3±1.1 ng/ml, P <0.05. At the same time, vitamin D deficiency was detected in 43.4% of children and adolescents without endocrine pathology. In the group with thyrotoxicosis, vitamin D deficiency was diagnosed in 84.2%, and its deficiency in 15.8% of pediatric patients. The average level of parathyroid hormone in the control group was 49.2±2.3 ng/ml, whereas, in the group with thyrotoxicosis, the average level of parathyroid hormone was significantly lower and amounted to 45.1±3.9 ng/ml, P<0.05. In the group with thyrotoxicosis, hypoparathyroidism occurred 4.9 times more often than among healthy children, 21.1% showed an increase in PTH levels of more than 65 ng/ml. According to the results of dual-energy X-ray absorptiometry in children and adolescents with thyrotoxicosis, the mean valuesand median of the Z-index of femoral neck, lumbar vertebrae and the total body were significantly lower than in the control group. In this control group, 4.2% of adolescents were diagnosed with juvenile osteoporosis. At the same time, in the group with thyrotoxicosis, 36.8% registered osteoporosis, P≤0.01.Thyrotoxicosis in children and adolescents causes a decrease in BMD and increases the development of osteoporosis by almost nine times. Thus, thyrotoxicosis in children and adolescents causes a decrease in bone mineral density and is accompanied by hypoparathyroidism and vitamin D deficiency.
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AEP194

Assessing risk factors and predictors of mortality in patients with fragility hip fracture
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Introduction
Fragility fractures are the main consequence of osteoporosis. It results in increased morbidity and mortality. The incidence of fractures has been increasing steadily in Portugal. Hip fragility fractures have been estimated to occur in up to 572/100,000/year in women and up to 232/100,000/year in men.
Methods
A retrospective study of hospitalized patients for femoral neck fracture in our institution in 2018 was performed to evaluate their previous risk of fracture and the predictive factors of one-year mortality. We excluded patients without a fragility fracture or absence of relevant clinical data. The previous absolute risk of fracture was calculated using FRAX-Port. High ten-year fracture risk (without BMD) was considered from 11% for major osteoporotic fracture and from 3% for hip fracture, according to 2018 Portuguese recommendations for the prevention, diagnosis and management of primary osteoporosis. Logistic regression was performed to evaluate factors associated with the occurrence of death and included also other risk factors not assessed in FRAX.
Results
We included 193 patients, with a median age of 84.0 years old (IQR 10) and 76.2% were female. Most patients (95.3%) underwent surgery after hospital admission. Globally they were hospitalized for a median of 9 days (IQR 8). They presented a median BMI of 24.44 kg/m^2 (IQR 6.18), 42% had a previous fragility fracture, 4.1% were smoker at the time, 5.2% had alcohol abuse, 4.7% were under therapy with glucocorticoid, 2.6% had rheumatoid arthritis and 4.7% had a disorder associated to secondary osteoporosis according to FRAX. The majority of patients (77.7%) did not perform previous dual-energy x-ray absorptiometry, even the ones with risk factors for fractures not included in FRAX. Median FRAX was 15.0% (IQR 11) for major osteoporotic fracture and 6.8% (IQR 7) for hip fracture. High absolute risk of fracture without BMD was found in 84.5% of patients. Only 14 patients were under osteoporosis treatment at the time of the fracture and other 14 were under calcium and vitamin D supplementation alone. All-cause mortality was 4.1% in the first 30 days and 19.2% in the first year. The risk of death was 3 times higher in men versus women (OR=3.223, 95% CI=1.281-8.107, P<0.013). It was also positively correlated with age (OR=1.082, 95% CI=1.019-1.149, P<0.011).
Conclusion
Fragility fractures are a dramatic public health problem. This study highlights the importance of the risk fracture evaluation, institution of preventive measures and close follow-up of patients suffering a fracture, given the high rate mortality.
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AEP195

Bone quality is associated with perinatal nutritional manipulation in adult Wistar rats offspring
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Introduction
Prenatal and perinatal food manipulation might be related with bone quality in offspring of Wistar rats. This study aimed to assess the impact of different dietary patterns provided before delivery to the mothers on the skeletal characteristics of newborn rats and the levels of insulin.
Materials and methods
We randomized 67 timed-pregnant rats into control diet (CD), high-fat (FD) and food-restricted (FR) on the 12th day of gestation. The pregnant Wistar rats delivered 618 pups on the 21st day. We classified pups born to FR-mothers, based on their birthweight, into fetal-growth restricted (FGR) and non-FGR. Following delivery, we enforced postnatal food manipulation

for all pups; the pattern of cross-fostering consisted of the offspring of CD-mothers being now lactated by FD, FR or CD fed dams. A similar process was applied for offspring of FR and FD-mothers. All pups were weaned to the diet of their fostered mother, starting from the 26th postnatal day until their 1st year of age, when they were sacrificed. We measured biochemical parameters and skeletal properties, using peripheral quantitative computed tomography.
Results
FGR-pups that received CD after birth had better skeletal properties compared to FGR-offspring that were starved postnatally and lower values of total/subcortical area compared to controls. Offspring fat-restricted postnatally had better skeletal properties if born to mothers who received high-fat diet compared to mothers who were food restricted during gestation. Higher levels of insulin were evident in pups born to mothers who received high-fat diet during gestation, provided pups received high-fat diet rather fat-restriction after birth.
Conclusion
The results of this study confirm the significance of intrauterine diet for the establishment of appropriate skeletal properties of the neonate. Islet dysfunction and predisposition towards raised insulin production during lifetime is linked with high-fat intake both before and particularly after birth.

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AEP196

Epidemiology of osteoporotic hip fracture in the largest urban area of Romania

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Background
Osteoporotic hip fracture remains a problem of public health concern. Different studies highlighted the existence of a particular epidemiology derived from local differences. We aimed to evaluate the epidemiology of osteoporotic hip fracture in the capital city of Romania plus city suburban area.
Methods
We collected data from over 95 % of fractures from hospitals with an Orthopedic Surgery Department in the area of interest. Patients were selected using the hip fracture codes (S72.0, 1, 2, 3, 7, 8, 9) and age >40 years old, during a 12 months period (09/01/2017 – 08/31/2018). We included only osteoporotic hip fracture (fall from a standing height or less) after a careful review of all the patients' medical records.
Results
We included a total of 1896 patients with fragility hip fracture (86.6% in the capital city and 13.4 % in the suburban area). 73.68% were female (mean age of 80.16±9.8 years old) and 26.14 % males (mean age of 75.85±12.2 years). The median body mass index was 23.87 kg/m^2 with only 21.5 % of the patients being overweight or underweight. Fractures in the femoral neck comprised 36.33 % of the total, intertrochanteric ones 55.74 %, atypical 6.8 % and 0.5 % nonspecific. Out of the total number, only 80.74 % were surgically treated (71.9 % of the femoral neck fracture, 86% of the intertrochanteric fractures and 90.7 % of the atypical ones). The median day of surgery after admission was 3±3.42 days (3.93±4 days for neck fractures and 2±2.94 days for intertrochanteric). 10.91 % of the patients had a history of one or more osteoporotic hip fracture.
Conclusion
This is the first study to describe the epidemiology of osteoporotic hip fracture in Romania after singly reviewing all patients' charts. Compared with literature data we discovered a very high rate of conservative treated fractures, and also a delayed time of surgery. We need further studies to evaluate the impact of this factors on the mortality rate.

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AEP197

The osteoporosis and hormonal status of our thalassemia patients

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Introduction
Thalassemia manifests clinically as anemia requiring life-long blood transfusions and the chronic iron deposition . Iron overload can lead to decreased functioning of the respective systems. Thalassemia-associated osteoporosis constitutes a majorproblem. Weinvestigated the bone mineral density scores of the thalassemic patients and correlated the scores of themwith some parameters including the transfusion frequency, levels of ferritin and pituitary hormones.
Subjects-materials
We recruited 54 thalassemic patients who were under follow-up in our hospital.26 of them were male, 28 were female. The mean of their age was 27.0±8.4 years, body weight 52.1±8.6 kg, transfusion frequency every 3.07±0.71 weeks, calcium (Ca) corrected for albumin 8.9±0.42 mg/dl, 25-0 h-vitamin D 321.9±10.5 ng/ml, total bilirubin (tot bil) 3.00±1.8 mg/dl, magnesium (Mg) 2.00±0.1 mg/dl, free triiodothyronine (f T3): 3.13 (OR:0.41, P=0.003) 0.62 ng/dl, prolactin 13,6±6.0 ng/ml, cortisol 11.2±2.9 mg/dl, Luteinizing hormone (LH): 2.5±1.7 IU/l, alkalen phosphatase 91.6±35.7 U/l, hemoglobin 9.3±0.7 g/dl, ferritin 1918.8±2188.3 ng/ml, mean corpuscular volume(MCV): 80.4±4.4 femtoliter/cell (fL), mean platelet volume (MPV) 7.39±1.88 fL, low density lipoprotein (LDL) 50.4±27.8mg/dl, high density lipoprotein (HDL):32.1±10.7 mg/dl, total cholesterol :107.9±33.5 mg/dl, Lumbar spine1-4 (L1-L4)T score –2,1±1.2, femoral total T score -0.7±1.4, femoral neck T score -0.7±1.5. When correlation analysis was attempted L1-L4 T score was correlated with Mg level [Odd's ratio (OR): 0.35 (P=0.021)], cortisol level (OR: –0.74, P=0.00), ferritin (OR: –0.38, P=0.007) and body weight (OR: 0.73, P =0.036). Femoral total T score was correlated with tot.bil. (OR: 0.41, P=0.003), MCV:f T3 (OR: 0.77, P =0.014), LH (OR: 0.73, P=0.033), LDL (OR: –0.42, P=0.003), total cholesterol (OR: –0.44, P=0.002), MCV (OR: –0.38, P=0.008). Seven (25%) female described amenorrhea,while one male (3.8%) had azospermia, one had decreased (3.8%) and two (7.7%) had increased total testosterone levels. Three (5.5%) patients had low IGF1 levels whose growth hormone levels showed normality after insulin tolerance test. Two patients experienced lumbar vertebralheight loss (3.7%) while one developed (1.8%) clavicle fracture. One patient (1.8%) had hypothyroidism under hormonal treatment while two (3.7%) had type1 diabetes mellitus.
Conclusion
The frequent endocrine complications reported in the literature in thalassemia are growth retardation, delayed puberty, hypogonadism, diabetes, impaired thyroid functions, and dyslipidemias. Early recognition and treatment of endocrine complications is important. A decrease in bone mass alsocan occur due to increased bone resorption or decreased bone formation which can lead to osteopenia/osteoporosis in thalassemia . The bone mass would be affected from several types of variables differing for separate parts of the skeleton thatconstitutesof L1-L4 vertebra and femur in our study . Transfusionnormalizing hemoglobin levels, iron chelation, and adequate hormonal,Vitamin D and calcium replacement therapy would reduce progressive bone disease.

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AEP198

Follow-up report: A case of FGF23-related tumor-induced osteomalacia with pulmonary adenocarcinoma

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Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome caused by the abnormal production of fibroblast growth factor 23 (FGF23) in the tumor. We havereported a case of TIO with pulmonary adenocarcinoma at ECE2018. Here we present the follow-up report of the case. A 61-year old woman suffering from severe polyarthralgia and bilateral limb weakness was referred to our hospital. Her blood chemistry revealed high alkaline phosphatase, low phosphate, low calcium, and low 1,25-$(OH)_2D_3$. Bone-scintigraphy revealed multiple accumulations, suggesting small fractures and systemic arthritis. Endocrinological analyses exhibited elevated iPTH and markedly high FGF23 level of 3900 (reference: 14.7–40.5) pg/ml.

These findings suggest that the FGF23-producing tumor induced osteomalacia. DOTATOC-PET/CT showed a major uptake in a nodular lesion of the left lung and several minor uptakes in the supraclavicular, hilar and mediastinal lymph nodes. An ultrasound-guided fine needle aspiration biopsy of the left supraclavicular lymph node revealed metastatic adenocarcinoma with a mutation in Exon19 of the EGFR gene. She was diagnosed as stage IV A (cT1cN3M1b) pulmonary adenocarcinoma, and the chemotherapy with afatinib maleate (EGFR tyrosine kinase inhibitor) was started. Simultaneously, alfacalcidol and menatetrenone were prescribed for osteomalacia. Five months later, the primary tumor and metastatic lesions gradually shrinked. The bone metabolism was almost normalized, the bone mineral density measured by DXA was improved, and FGF23 level was markedly decreased to 42 pg/ml. The arthralgia was ameliorated and controlled with minimal dose of analgesics. After the partial remission for 16 months, the metastatic lesion progressively enlarged and FGF23 was slightly elevated to 66 pg/ml. The anticancer agent was switched to osimertinib mesilate. Three months later, the lesion contracted again and FGF23 level was decreased to 34.7 pg/ml. At present, 35 months after the first visit, she is still in partial remission and working as a housewife. This is a rare case of TIO associated with pulmonary adenocarcinoma.

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AEP199

Biochemical and clinical findings distinguishing between the genetic and the acquired conditions in osteoporotic patients with low serum alkaline phosphatase levels

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Background
Hypophosphatasia is a rare genetic disease with low serum alkaline phosphatase (ALP) activity and hypophosphatasemia. It is caused by loss-of-function mutations and deletions of the tissue-nonspecific isoenzyme of alkaline phosphatase (*TNSALP*) gene; it has a wide range of severity in its phenotype, from death in utero to asymptomatic disease accidentally diagnosed in adult life. Furthermore, some diseases and drugs may induce hypophosphatasemia. Thus, the genetic and acquired etiology can be hardly distinguishable. Aim of the present study was to identify clinical and/or biochemical parameters predictive of genetic disease.
Materials and methods
This is a retrospective study. Biochemical analyses, including serum vitamin B6 and urinary phosphoethanolamine, DXA results and genetic analyses (NGS, MLPA and direct sequencing) were performed in 21 adults (0.9%) with at least two values of ALP below the reference levels out of 2319 osteoporotic patients referred to our third level Bone Unit. Hypophosphatasemic patients with diseases and therapies known to reduce ALP levels were excluded.
Results
Eight patients harboring mutations and/or polymorphic variants of the*TNSALP* gene (two males, six females; median age 55.0 years, range 50.9–65.6: group A) were detected. Thirteen patients (three males, Ten females; median age 51, range 45.4–62.2) had a negative genetic molecular analysis (group B). The two groups were similar for most of the investigated biochemical parameters, including vitamin B6 levels, though urinary levels of phosphoethanolamine showed the trend to be higher in the group A patients [median values 5.25 (3.22–6.10) vs 3.0 (2.30–4.85) mmol/mol of creatinine; $P=0.056$]. On the other hand, anamnestic data appear more indicative of the genetic origin of hypophosphatasemia: dental anomalies, musculoskeletal symptoms and familiarity for skeletal and extra-skeletal manifestations of the disease occurred more frequently in group A with respect to group B ($P=0.056$, $P=0.032$, and $P=0.032$, respectively). It is note of worth that 7 out of the 13 patients harboring the wild type *TNSALP* gene experienced low levels of ALP during treatment with tamoxifen, a drug whose hypophosphatasemic effect is uncertain.
Conclusions
Urine levels of phosphoethanolamine may be a useful tool in distinguishing between genetic and acquired forms of hypophosphatasemia, though anamnestic data such as dental anomalies, musculoskeletal symptoms and familiarity for the skeletal and extra-skeletal manifestations of the disease may be even more relevant in the selection of the patients deserving of genetic analysis. Moreover, our data suggested that tamoxifen should be considered as a hypophosphatasemic drug.

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AEP200

Multiple vertebral fractures in a real-life denosumab-treated cohort: Patient level data

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Introduction
Denosumab discontinuation rapidly reverses bone turnover inhibition and eliminates anti-fracture protection. Multiple vertebral fractures (MVF) were reported in this scenario. Previously, we reported a retrospective real-life analysis designed to estimate fracture risk following denosumab discontinuation. Here we report a patient-level data of a subgroup with MVF.
Methods
Via computerized database of Maccabi Healthcare Services, persistent denosumab users (PU) and denosumab discontinuers (DD) were detected. MVF were adjudicated by an expert's chart review. Patients' baseline characteristics, osteoporosis therapy, variables related to denosumab treatment and discontinuation, and post-MVF treatments were retrieved.
Results
In the core study, 12 female patients with MVF were identified among 1500 DD (MVF-DD) and 2 among 1610 PU (MVF-PU), $P<0.01$. The MVF patients were comparable in age (71 ± 12 vs 68 ± 11), BMI (26.4 ± 2.9 vs 22.6 ± 2) and eGFR (73 ± 27 vs100 ± 7.7) among DD and PU, respectively. Osteoporotic fractures prior to denosumab treatment were prevalent in 41.6% MVF-DD and 100% MVF-PU ($P=0.4615$). Femoral neck T-scores were -2.7 ± 1 vs -3.5 ± 0.56 ($P=0.33$) in the MVF-DD and MVF-PU, respectively. 75% of MVF-DD versus 100% of MVF-PU received osteoporosis medications prior to denosumab. MVF occurred 134 ± 76 days post DD and 57 ± 35 days from the last dose in PU. Two patients in the MVF-DD passed away. One patient suffered from additional VF. Denosumab, teriparatide, oral and IV bisphosphonates were prescribed in various sequences post-MVF and two patients underwent vertebroplasty/kyphoplasty.
Conclusions
MVF occurred in high-risk individuals in both groups. There is no consistency in post-denosumab discontinuation management and studies are urgently needed to reveal the safest approach. Denosumab discontinuation should be avoided, especially in patients with high-risk profile.

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AEP201

Body composition and bone mineral density in craniopharyngioma patients: A longitudinal study over 10 years

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Introduction
Patients with craniopharyngioma (CP) suffer from pituitary deficiencies and hypothalamic damage, resulting in obesity and impaired bone health. Little is known about long-term changes in body composition and bone mineral density (BMD).
Methods
Dutch and Swedish patients were included in this retrospective longitudinal study if they had DXA-scan (body composition/BMD) data available at

age of 18 years or older. Linear regression modelswereestimated for change of Z-score of total body, L2-L4 and femur neck. Age- and sex-specific standardized deviation scores (SDS) were calculated. Data is provided as mean±standard deviation unless stated otherwise.
Results
There were 112 CPincluded [58 (52%) male, 50 (44%) childhood-onset] witha median age at first presentation of 25 years (range 0–73) and median age at last documented visit at the clinic of 49 years (range 16–82). All patients had one DXA-scan available, 86 CP had at least two DXA-scans. The mean time between first and last DXA-scan was 10.8±6.7 years. Hypopituitarism occurred in 96%. Values of body composition measures were high and increased: BMI at first DXA-scan was 30.0±4.8, the mean difference from first to last DXA-scan 1.95±3.39, P<0.001. Fat mass index (FMI) at first DXA-scan was 10.7±3.4, the mean difference to last DXA-scan was 0.86±2.41, P=0.002; fat free mass index (FFMI) at first DXA-scan was 18.3±3.2; the mean difference to last DXA-scan was 18.3±3.2, 1.15±1.86, P <0.001. However, corresponding SDS did not increase, except for FFMI SDS (from 0.26±1.63 to 1.11±2.14, P<0.001). Fat percentage (SDS) did not change. Predictors in a linear regression model for Z-score models were hydrocortisone dose (total body Z-score: beta –0.07, P=0.002), medication to improve BMD (L2-L4 Z-score: beta -1.07, P=0.008), radiotherapy (femur neck Z-score: beta –0.64, P=0.04); the estimated regression coefficient for growth hormone replacement therapy was not significant but showed a strong trend (femur neck Z-score: beta 0.81, P=0.06).
Conclusions
Patients withCP remain stable in BMI SDS, fat percentage SDS and FMI SDS and increase in FFMI SDS and BMD Z-scores. Hydrocortisone dose, radiotherapy and medication to improve BMDwere significantly associated to change in BMD (Z-score).Growth hormone replacement therapy showed a trend towards association with Z-score.

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AEP202

Body composition and adipokines influence upon bone mineral density and bone metabolism in renal transplant receivers

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Introduction
Renal transplant receivers (RTR) have a higher risk for osteoporosis, obesity and sarcopenia, which all seem to be interrelated. FGF23 and adipokine disorders, often recognized in RTR, might be involved in the fat-muscle-bone crosstalk. The current study aims to evaluate the influence of body compartiments and adipokines on bone mass in RTR.
Methods
Thiscross-sectional study investigates the predictive role of body composition, adipokines (leptin, adiponectin, resistin) and FGF23 upon bone mineral density (BMD) and bone metabolism parameters (osteocalcin, C-terminal telopeptide of type I collagen (CTx), calcium, phosphate) in 59 RTR and 59 age, sex and BMI-matched healthy controls, using correlation and multiple linear regression analysis.
Results
Comparative analysis of the two groups confirmed lower BMD in the RTR group at the hip, neck, forearm and whole body locations (P<0.005). In the RTR group, mean GFR was 53.93±23.98 ml/min/1.23 m^2, 86% have osteoporosis, 13.6% have sarcopenia and 47.5% are overweight.
Total lean mass (TLM), lean mass index (LMI) and appendicular lean mass index (ALMI) were mildly positively correlated with all bone parameters (P<0.001 for all). Fat mass percentage (FM%) was a negative predictor for BMD at the level of forearm (Coef R2=0.152, P=0.002) and whole body (Coef R 2=0.098, P=0.016).
Negative correlations were found between adiponectin, resistin, and lumbar and forearm BMD, respectively (P<0.05). Adiponectin is also positively correlated with osteocalcin (r=0.540, P<0.001), but negatively associated with CTx (r=–0.375, P=0.007). Leptin negatively impacts forearm (r=–0.449) and whole body BMD (r=–0.419) (P<0.005 for all) and is positively correlated with osteocalcin (r=0.280, P<0.05). No relationship was observed between serum FGF-23 or klotho levels and BMD values.
TLM and FM% remained the only independent predictors of forearm, hip and whole-body BMD inmultiple regression analysis (P<0.001) after adjusting for confounders such as age, sex, cumulative dose of corticosteroids, dialysis time period, smoking, adipokines levels, graft function.
Conclusions
This is the first study confirming the predictive role of TLM on BMD after renal transplantation, with predilection at the forearm level. Adipokines interfere with bone remodeling, both leptin and adiponectin being associated with higher levels of bone formation markers andlower level of bone resorbtion markers. Their overall negative effect on bone mineral density implies a compound effect yet to be determined.

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AEP203

Hip spine discordance in bone mineral density: Prevalence and potential significance

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Introduction
The WHO recommends that osteoporosis be diagnosed based on the lowest T score in hip, spine or distal 33% radius. Indian guidelines emphasize T score based diagnosis and treatment of osteoporosis..One of the reasons for measuring bone density is to account for differences in bone density between sites. The data on discordance in bone density between the hip, spine and distal radius is scarce in India - despite DXA scanning being available in India for the last 20 years. If there's a significant discordance between hip and spine, this can potentially have impact on the diagnosis of osteoporosis. With the currently available options for treatment of osteoporosis, such discordance would raise the question of selective targeting of hip or spine, depending on bone density. Thus it is important to know the prevalence of clinically meaningful discordance and its predictors in Indian patients.
Materials and methods
This was a retrospective study in which individuals who underwent BMD measurement and FRAX scoring at Sri Ramachandra Medical Centre, Chennai during the time period July 2016 to July 2018 were included. Those who have already received treatment with US Food and Drug Administration (USFDA) approved drugs for osteoporosis were excluded. Height and weight were measured using standard medical scales. Femoral neck BMD and T-score were obtained from the DXA scanner. DXA was done using the same machine for all the subjects (GE Lunar Prodigy Advance enCORE™ Version 13.60).
Discordance in the classification between hip and spine was noted. Minor discordance was defined as one step classification difference (Normal in one site and osteopenia in the other or Osteopenia in one site and osteoporosis in the other). Major discordance was defined as maximum difference in classification between sites – normal in one site and osteoporosis in the other. The analysis was repeated with ICMR normative data. Ordered logistic regression, with all the variables used in FRAX calculation, was used to identify predictors of discordance.
Results
The study included 808 adults, both men and women, above the age of 50. The mean age(sd) was 58.7 (6.2) years. The group had 56.8% men. None of the patients were taking any osteoporosis medications. In 58.2% of patients, no discordance was seen. In 2% of patients major discordance was seen and 39.9% of patients had minor discordance.
Conclusion
Hip spine Discordance is seen in 4 out of 10 patients undergoing DEXA scan.

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AEP204

High serum FSH is not a risk factor for low bone mineral density in infertile men

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Background
Male infertility is associated with a higher long-term morbidity and mortality risk. However, it is not clear which diseases are contributing to this risk. Osteoporosis is a possible factor, as it is a frequent disease and sex steroids regulate both fertility and bone health. Furthermore, there are data indicating that high FSH levels in women are related to low bone mineral density (BMD), independent of estradiol levels. As infertile men often have increased FSH, already from a young age, this could be a risk factor for impaired bone health in later life.
Methods
One hundred and thirty-seven men with a history of male factor infertility due to spermatogenic failure (SgF men) as well as a control group of 70 men from couples treated with IVF for female factor infertility (non-SgF men) were included in a long-term follow-up study. Men with explained infertility, including testosterone deficiency, were excluded. Data from baseline fertility investigations were retrieved from the patient files of the SgF men. At follow-up, hormonal and semen analysis was performed and axial, femoral and total body BMD was measured by dual X-ray absorptiometryin all men. Multiple linear regression was used to assess differences between SgF and non-SgF men and to study associations between FSH levels and BMD.
Results
Median follow-up time was 14.8 years (5th-95th percentile 11.3–18.2) after fertility assessment for SgF men and 15.6 years (12.1–18.5) for non-SgF men ($p=0.033$). When comparing the two groups, no significant differences in total T, free T or E2 levels were apparent at follow-up. As expected, LH and FSH were higher in SgF men (median (5th–95th percentile)) for LH (IU/l): 4.3 (2.2–13.6) for SgF men and 3.0 (1.4–5.8) for non-SgF men ($P<0.001$); FSH (IU/l): 9.8 (2.8–35.5) vs 3.7 (1.6–8.7); $P<0.001$). Inhibin B and semen parameters were lower in SgF men.
There were no differences in BMD between the two groups. Furthermore, both groups had median Z-scores close to zero at all sites, indicating that BMD is not different when compared to age-matched healthy men. In SgF men, neither baseline FSH, nor FSH at follow-up, was associated with BMD at the different sites at follow-up.
Conclusion
Men with spermatogenic failure are not at increased risk for impaired bone health later in life. Furthermore, infertile men with high FSH levels do not have lower BMD.

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AEP205

Denosumab-induced hypocalcemia: Does gender play a role?

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Introduction
The recognition that disease presentation, treatment and outcomes may differ betweenmen and women has become established. We have recently reported a-7.4% rate of denosumab-associated hypocalcemia in community-dwelling osteoporotic patients.
Aim
To investigate the role of gender in this complication.
Methods
A retrospective analysis of medical records (2010–2018) from a large HMO. An albumin-adjusted serum calcium concentration ≤8.5 mg/ml was defined as hypocalcemia.
Results
A total of 1871 women and 134 men were included. Men were older (median 81 vs 77 years, $P=0.004$), more likely to receive denosumab as first-line treatment (22% vs 6%, $P<0.001$), were treated less with calcium supplements (42% vs 53%, $P=0.024$) and had a lower median eGFR level compared to women (66.1 vs 79.9 ml/min/1.73m^2, $P<0.001$).Denosumab-associated hypocalcemia developed in 133 women (7.1%) and in 16 men (11.9%) ($P=0.04$). The strongest predictors of hypocalcemia in women were pretreatment levels of albumin-adjusted serum calcium (OR 0.08, 95% CI [0.04, 0.14]) and creatinine (OR 2.43, 95% CI [1.45, 4.05]). There were no predictors for hypocalcemia in men, probably due to the small cohort. Gender was not a predictor for hypocalcemia after propensity matching of 126 men versus 126 women.
Conclusion
Contrary to previous reports, male gender *per se* is not a risk factor for denosumab-associated hypocalcemia. Despite increasing recognition of male osteoporosis, there was a considerable difference in the number of treated men and women. Men who received denosumab were significantly older with lower GFR, therefore are probably more prone to develop hypocalcemia.

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AEP206

Parathyroid carcinoma: An italian multicenter retrospective analysis

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Parathyroid carcinoma (PC) is a rare neoplasia responsible for about 1% of primary hyperparathyroidism (PHPT). Differently from patients with its benign counterpart, the phenotype of these patients is characterized by severe PHPT and hypercalcemia. The aim of this study was to describe a series of PC casesrecorded in the regional cancer network of Piedmont and Valle d'Aosta, Italy (Rete Oncologica del Piemonte e della Valle d'Aosta) from 2007 to 2017, including 25 patients (11 males and 14 females, mean age 59 yrs) from four hospitals (AO S. Croce e Carle in Cuneo, AOU Città della Salute e della Scienza and ASL Città di Torino in Turin and AOU Ospedale Maggiore della Carità in Novara). Disease incidence, gender, age at time of diagnosis, presence of renal and bone symptoms, serum calcium and PTH levels, surgical technique performed and percentage of recurrence were analysed. A PC incidence of 0.05 cases per 100.000 inhabitants was found in this region. PC occurred equally in males and females and affected patients mostly in their fifties. Concomitant hypercalcemia and increased PTH were present in all patients. Typical PHPT symptoms were reported in 92% of PC cases. In this series, en-bloc resection showed a 13 times lower risk of relapse compared to all the other surgical techniques. A not-radical surgical resection is associated with a higher recurrence rate. In conclusion, this series confirms that PC is equally gender distributed, with average age at diagnosis earlier than benign PHPT. A meticulous pre surgical evaluation of PHPT patients who show evocative features of PC is mandatory in order to adopt an appropriate approach and treatment of this disease.

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AEP207

18Fluoro-choline PET/CT is a useful tool for patients with primary hyperparathyroidism negative at first-line imaging localization tecniques

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Primary hyperparathyroidism (PHPT) is a common endocrine disease mainly caused by a single parathyroid adenoma. Although the localization of the parathyroid adenoma is not a surgical criteria for parathyroidectomy, this is known to increase the cure rate of PHPT and reduce the complication rate. Neck ultrasound and MIBI-scintigraphy are the first-line localization techniques to detect parathyroid adenomas, however, they have some

limitations including the operator-dependent sensitivity and limited utility in case of a deep-laying or ectopic parathyroid. Scintigraphy is better for ectopic localizations but its sensitivity remains suboptimal. Evidence has recently emerged that parathyroid adenomatous cells are capable of capturing choline similarly to what occurs in prostate cancer, making this molecule a potential tracer in parathyroid. We conducted a monocentric study at theUniversity Hospital of Pisa in order to evaluate the utility of ^{18}Fluoro-choline PET/CT in 20 patients with PHPT candidates for surgery and with negative or inconclusive conventional imaging. All patients underwent a neck ultrasound performed by an expert physician in parathyroid disease and a double tracing MIBI SPECT/CT. Neck ultrasoundwas negative in 15/20 patients and uncertain in 4. SPECT/CT was negative in 18/20 and uncertain in 2 patients. Therefore, 18F-choline PET/CT (with early and late scans and without iodinated contrast) was performed in the whole group. A dosimetric study was done: 18F-choline PET/CT effective dose was 8.09 mSv. Twelve patients (60%) were positive, 4 (20%) inconclusive and 4 negative. Eleven patients underwent surgical removal of the lesion detected at PET/CT, of which eight with mini-invasive approach and three with an open cervicotomy due to a concomitant thyroidectomy for non toxic multinodular goiter. In all cases histology showed a parathyroid adenoma (mean size 7,3 cc, range 0.4–33.5 cc). An intraoperative PTH assay was performed in 9 cases and in all demonstrated a reduction greater than 50% of PTH levels from the highest basal value. Disease cure was confirmed in all patients after 1 month post-surgery and no surgical complications were recorded. In our experience, therefore, 18F-coline PET/TC has demonstrated a good diagnostic performance and a valid alternative in patients having negative/inconclusive conventional imaging. Furthermore, it has allowed us to avoid bilateral cervical exploration in the patients. Finally, compared to four dimensional (4D) CT, another emerging imaging method for parathyroid glands, 18F-coline PET/CT exposes the patients to less radiation (CT 4D effective dose is at least 27 mSv) and does not require the use of iodine contrast.

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AEP208

Effect of vitamin D supplementation on carotid intima media thickness in overweight and obese schoolchildren: A single blind randomized clinical trial

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Previous observational studies suggest that low 25(OH)D concentrations in childhoodmight have deleterious effects on vasculature. The present study addresses this key knowledge gap with the use of a dose-response randomized clinical trial (RCT) aimed to determine the effect ofone-year vitamin D supplementationon carotid intima media thickness (cIMT) in overweight and obese school children. The current study was a single-blind RCT. A total of 378 children and adolescents, 6–13 y of age, with age- and sex-specific body mass index (BMI) Z-score ≥ 1 (according to the World Health Organizationcriteria)were recruited into the study. Participants were allocated to receive 600, 1000, and 2000 IU/d for 12 months. We measured cIMT at baseline and end of 12 months. In this intention-to-treat analysis, to estimate the effect size of 1000 and 2000 IU/d vitamin D in comparison to 600 IU/d, we fit a linear mixed effect model adjusted for sex, season of recruitment, and baseline cIMT, smoking exposure, physical activity, puberty status, and BMI. Participants' mean (SD) age was 9.3 (1.7) y; 52.3% wereboys with BMI z scores of 2.55(0.73). The mean (SE) for 25(OH)D were 13.7 (0.79), 14.8 (0.86), 14.8 (0.79) ng/ml at baseline (P=0.792) and 22.7(0.57), 26.1 (0.70), 30.2 (0.78) ng/ml at the end of 12 months (P<0.0001) in 600, 1000, and 2000 IU/d, respectively. The standardized mean difference (95% CI) after adjusting covariates was 0.36 (0.07, 0.65) and 0.97 (0.67, 1.28) for 1000 and 2000 IU/d vitamin D, respectively. The mean (SE) for cIMT were 0.396 (0.005), 0.403 (0.005), 0.406 (0.005) mm at baseline (P=0.389) and 0.400 (0.008), 0.405 (0.009), 0.407 (0.007) mm at the end of 12 months in 600, 1000, and 2000 IU/d, respectively (P=0.821). The cIMT change during one-year follow-up was not significant between three groups. The standardized mean difference (95% CI) after adjusting covariates was –0.0003 (–0.294, 0.293) and 0.081 (–0.207, 0.370) for 1000 and 2000 IU/d vitamin D, respectively. In conclusion, children with excess weight did not benefit from daily supplementationof 1000 and 2000 IU/d for one year compared with 600 IU/din decreasing subclinical atherosclerosis; although 25(OH)D increased.

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AEP209

Can serum calcium, phosphorus and parathyroid hormone levels predict histopathological diagnosis in patients with primary hyperparathyroidism?

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Aim
While the histopathological diagnosis is parathyroid adenoma in majority of patients with primary hyperparathyroidism (PHPT),parathyroid hyperplasia, atypical parathyroid adenoma or parathyroid carcinoma can be seen in others. Although it is known that serum calcium (Ca) and parathyroid hormone (PTH) levels are higher in patients with parathyroid carcinoma, there are not any cut-off value for serum Ca, phosphorus (P) and PTH levels defined for different histopathological parathyroid lesions. In this study, we aimed to determine cutoff levels for serum Ca, P and PTH in different histopathological PHPT lesions.
Materials and Methods
The data of 392 patients operated for PHPT were evaluated retrospectively. Patients were grouped as parathyroid hyperplasia, parathyroid adenoma and atypical parathyroid adenoma according to histopathological results. Three way ROC analysis was used to evaluate the performance of serum Ca, P and PTH to determine the three groups. It was shown that Volume Under Surface (VUS) higher than 0.17 was giving information beyond chance. Cut-off levels and correct classification rates (CCR) were calculated when the VUS value was significantly higher than 0.17.
Results
There were 19 patients with parathyroid hyperplasia, 343 with parathyroid adenoma and 31 with atypical parathyrod adenoma. Serum Ca, P and PTH levels were significantly different between groups (P=0.026, P=0.003 and P≤0.001, respectively). Serum Ca was significantly lower in parathyroid hyperplasia group compared to other two groups (P=0.032 and P=0.036, respectively). Serum Ca was similar in patients with parathyroid adenoma and atypical parathyroid adenoma (P=0.999) (Table 1). The performance of serum P and PTH to determine groups were not sufficient significantly (P >0.05). In determining the groups, only the VUS value of serum Ca was statistically significantly higher than 0.17 (P=0.005). The cut-off values for the variable were determined as C_1=10.73 mg/dl and C_2=11.40 mg/dl, respectively.
Conclusion
In this study, we found that serum Ca levels can be predictive for the histopathological diagnosis in patients with PHPT. Serum Ca lower than 10.73 mg/dl, 10.73–11.40 mg/dl and >11.40 mg/dl were determined to predict parathyroid hyperplasia, parathyroidadenoma and atypical parathyroid adenoma, respectively.

Table 1 Serum calcium, phosphorus and parathyroid hormone in patients with primary hyperparathyroidism according to histopathological diagnosis.

	Parathyroid hyperplasia (n=19)	Parathyroid adenoma (n=342)	Atypical parathyroid adenoma (n=31)	P
Calcium (mg/dl)	10.98±1.31	11.39±0.98	11.56±1.24	0.026
Phosphorus (mg/dl)	3.83±2.08	2.62±0.69	2.35±0.59	0.003
Parathyroid hormone (pg/ml)	806.71±923.07	229.82±311.67	402.54±383.46	<0.001

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AEP210

Is the assessment of clinical risk factors for vitamin D deficiency sufficient?

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Introduction
Extremely low levels of vitamin D usually include levels < 4 ng/ml, which is almost the same as undetectable. The risk groups for vitamin D deficiency have been identified, but do they allow such patients to be identified based solely on clinical presentation.
Objective
To identify risk factors and their actual clinical determination in patients with 25(OH)D serum levels <4 ng/ml.
Materials and methods
The study included electronic medical record information of 72 individuals (mean age 43 ± 3, 59 women and13 men) with a vitamin D level of < 4 ng/ml found among 5449 patients (1,3%) tested in 2019. Total 25(OH)D was determined using the immunochemiluminescent method. The laboratory participates in the DEQAS program.
Results
No clinical information was available for 20 patients so they were excluded from further analysis. Of the clinical risk factors among the rest 52 patients: 0 – had a dark skin tone, 0 had liver failure, 0 were pregnant, 13 – BMI more than 30 kg/m^2, 12 had diseases of bones or complaints of diffuse bone pain, 6 – GFR less than 60 ml/ml, 5 – primary hyperparathyroidism, 5 patients took drugs that distirb the metabolism/absorption of vitamin D. Nineteen of 52 (37%) patients did not have any risk factor for vitamin D deficiency according to their medical record.
Conclusions
Clinical evaluation of risk factors for vitamin D deficiency does not allow to correctly identify such patientswhich may necessitate thereview of the predisposing factors or be the basis for a wider biochemical screening.

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AEP211

First results of an austrian prospective hypoparathyroidism registry – the HypAus study

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Background
Permanent hypoparathyroidism is the most common complication of thyroid surgery with a reported incidence of 2-10% depending on the observation time, extent of surgery and underlying disease, with higher risk for total thyroidectomy and Graves disease/thyroid cancer. European data on chronic hypoparathyroidism have been reported from several countries, especially Scandinavia. We therefore aimed to add more information from Central Europe.
Methods
In this ongoing prospective Austrian multi-center observational registry at the Medical University of Graz and the Medical University of Innsbruck, we include adult patients with hypoparathyroidism of all etiologies. Routine clinical and laboratory data is collected for all patients. Extensive neurocognitive assessment with comparison to a normative collective is performed in a subgroup of patients and will be reported separately, including the Trail Making Test A and B (TMT-A and TMT-B).
Results
So far, we included 47 patients. 39 are women (83%), and the average age is 61 ± 17 years. 13% have nonsurgical etiologies (ie. AIRE or 22q11 mutations, "idiopathic"), and 87 % had postsurgical hypoparathyroidism. Both hypercalcemia and hypocalcemia were common. Paresthesia and tetany was reported by most patients. In postsurgical hypoparathyroidism, the median time between surgery and diagnosis of hypoparathyroidism was 5.5 years (range: 0–67 years). Treatment included calcium, active vitamin D, vitamin D, hydrochlorothiazide, magnesium and teriparatide. Three patients were started on rhPTH 1–84 (Natpar) since early 2018. TMT-A and TMT-B were performed in 15 patients and showed slower task resolution for TMT-A: 32 (IQR: 22–38) vs 29 seconds (IQR: 24–37), $P = 0.233$ and TMT-B (median = 78; IQR: 72–109 vs 58 seconds, IQR: 51–89, $P = 0.001$).
Conclusion
In this prospective registry, we report and continue to collect real-world data of hypoparathyroid patients in Austria with the goal to increase awareness and facilitate optimization of care of this rare disease.

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AEP212

Renal complications in patients with chronic hypoparathyroidism receiving conventional therapy: A systematic literature review

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Conventional therapy for chronic hypoparathyroidism is oral calcium and active vitamin D; despite treatment, chronic hypoparathyroidism may be associated with increased risk of renal complications. Without the effect of parathyroid hormone on renal tubular reabsorption, calcium-conserving and phosphaturic effects are lost, serum calcium levels are reduced and serum phosphate levels are increased. This may lead to hypercalciuria and hyperphosphataemia, which may be associated with long-term renal complications. A systematic literature review was performed to summarise the frequency and nature of renal complications in patients with chronic hypoparathyroidism managed with conventional therapy. Abstracts with specified MeSH terms were identified using the PubMed, EMBASE, and Cochrane databases. Pre-defined outcomes were nephrolithiasis, nephrocalcinosis, and chronic kidney disease (CKD). Papers that described estimated glomerular filtration rate (eGFR) were also selected. The search yielded 1200 articles; following screening and assessment for eligibility, 21 articles reported data for nephrolithiasis/kidney stones, nephrocalcinosis, and/or CKD. Data were extracted from 13 manuscripts with renal outcomes for ≥10 adult ($n = 11$ manuscripts) or paediatric ($n = 2$ manuscripts) patients. Some articles contributed to ≥1 outcome category. Due to the heterogeneity of the studies, a meta-analysis could not be conducted. The reported rate of nephrolithiasis was ≤36%, including 0% in the Levy et al paediatric study, with low rates in other studies reporting shorter duration of disease (Table). Nephrocalcinosis was ≤ 38%, with 2 studies reporting rates of 0% (Table). Nephrolithiasis and/or nephrocalcinosis was 19%–31%, and CKD/kidney failure/renal insufficiency 2.5%–41% (Table). Chronic hypoparathyroidism is a rare disease, which likely contributed to the heterogeneity in reported renal complications in this systematic literature review. Overall, however, patients with chronic hypoparathyroidism who receive conventional therapy had an increased risk of renal complications. Limitations of this systematic literature review are the differences in study design, heterogeneity in imaging methods, which may have affected detection/differentiation of small stones/parenchymal calcinosis, and heterogeneity in the methods of reporting renal outcome data. Additional large-scale studies are needed to understand how the disease pathophysiology and/or conventional treatment may increase the risk of renal complications in patients with chronic hypoparathyroidism.
Funding: Shire, a Takeda company

Table Renal complications in patients with chronic hypoparathyroidism.

Article Study Design	Patients, *n*	Mean ± SD Duration of Disease/Follow-up, years	Methods	Patients with Nephrolithiasis	Patients with Nephrocalcinosis	Patients with CKD/renal insufficiency*
Hadker N, *et al. Endocr Pract.* 2014;20(7):671–679 Patient self-reporting in a cross-sectional survey	374	Duration: 12.6 ± 12.4	Self-report; CKD reported as chronic kidney failure	35.5%	22% with severe HypoPT vs 6% with mild HypoPT (P ≤ 0.05)	19% with severe HypoPT vs 2.5% with mild HypoPT (P ≤ 0.05)
Meola A, *et al. J Endocrinol Invest.* 2018;41(10):1221–1226 Prospective study	90	Duration: 9 ± 7 Median (IQR) follow-up: 7.0 (4–11)	Renal ultrasound; CKD: CKD-EPI equation	30%	0	12%
Underbjerg L, *et al. J Bone Miner Res.* 2013;28(11):2277–2285 Retrospective follow-up study using national health registry data	688	Median (IQR) duration: 8 (4–12) Follow-up: 8.4	Determined by ICD-8 or ICD-10 codes; CKD reported as renal insufficiency	2%	Not reported	5%
Underbjerg L, *et al. J Bone Miner Res.* 2015;30(9):1738–1744 Retrospective follow-up study using national health registry data	180	Not reported	Determined by ICD-8 or ICD-10 codes; CKD reported as renal insufficiency	1%	Not reported	8%

Arit W, *et al. Eur J Endocrinol.* 2002;146(2):215–222 Cross-sectional study	25	Median (range) duration: 3 (0.5–38)	Renal ultrasound	8%	0	Not reported
Lopes MP, et al. Arch Endocrinol Metab. 2016;60(6):532–536 Retrospective observational study	55	Duration: 11.2 ± 7.5 Follow-up: Not reported	Renal ultrasound CKD: Cockcroft-Gault formula CKD stages per KDIGO	Nephrolithiasis and nephrocalcinosis reported combined: 25% (10/40 with imaging)		33% in stage 2 9% in stage 3 2% in stage 4 2% in stage 5
Leidig-Bruckner G, *et al. Horm Metab Res.* 2016;48(12):806–813 Retrospective, longitudinal chart review	33	Duration: 15.9 ± 9.4 Follow-up: 11.9 ± 6.6	Radiologic imaging (ultrasound, CT, and/or MRI); CKD:Cockcroft-Gault formula	Nephrolithiasis and nephrocalcinosis reported combined: 27% Partial HypoPT: 25% Complete HypoPT: 31%		Partial HypoPT: 5% Complete HypoPT: 23%
Mitchell DM, *et al. J Clin Endocrinol Metab.* 2012;97(12):4507–4514 Retrospective, longitudinal chart review	120	Duration of disease: 17 ± 16 Follow-up: 7.4 ± 5.1	Renal/abdominal ultrasound and abdominal CT; CKD: MDRD equation	Nephrolithiasis and nephrocalcinosis reported combined: 31% (17/54 with imaging)		41%
Astor MC, *et al. J Clin Endocrinol Metab.* 2016;101(8):3045–3053 Patient survey using hospital registry	283	Not reported	CKD: MDRD formula	Not reported	Not reported	18%
Underbjerg L, *et al. J Bone Miner Res.* 2018;33(5):822–831 Case-controlled retrospective study using national health registry data	431	Median (range), duration: 12.7 (0.5–87.1) Follow-up: Not reported	CKD reported as renal insufficiency	Not reported	Not reported	21%
Levy I, *et al. J Clin Endocrinol Metab.* 2015;100(11):4106–4113 Long-term retrospective follow-up study	29 (paediatric)	Duration: 9.1 ± 5.5 Follow-up: 7.4 ± 5.0	Renal ultrasound; CKD: eGFR (revised Schwartz estimating equation for nonchronic kidney disease populations)	0	38%	0 45% had avg eGFR 60–90 mL/min/1.73 m²
Kim JH, *et al. Clin Endocrinol (Oxf).* 2015;83(6):790–796 Long-term retrospective	37 (paediatric)	Follow-up: 7.0 ± 5.3	Renal imaging in 26 pts (conducted every ~2.5 y)	Nephrolithiasis and nephrocalcinosis reported combined: 19%		Not reported

Note: One study from the database search did not provide numerical data and is not included in this table (Bohrer T, *et al. Eur Surg.* 2007;39(1):39–44).
*CKD defined as < 60 ml/min/1.73 m² or <60 ml/min unless otherwise noted.
CKD = chronic kidney disease; CKD-EPI = chronic kidney disease epidemiology collaboration; CT = computed tomography; eGFR = estimated glomerular filtration rate; HypoPT = hypoparathyroidism; ICD = International Classification of Diseases; IQR = interquartile range; KDIGO = Kidney Disease Outcomes Quality Initiative; MDRD = modification of diet in renal disease; MRI = magnetic resonance imaging.

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AEP213

Renin-angiotensin-aldosterone system in patients with primary hyperparathyroidism

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Background
Hypertension is one of the widespread cardiovascular pathology in patients with primary hyperparathyroidism (PHPT).The renin-angiotensin-aldosterone system (RAAS) is a key system in the regulation of blood pressure and its interactions with mineral metabolism are described. Our previous study* of PHPT patients revealed a significant decrease in plasma renin activity (PRA) and serum aldosterone levels in the early postoperative period and also positive correlations of calcium and PTH with RAAS parameters.
The aim of this study was to investigate follow-up changes of the RAAS activity in PHPT patients one year after surgery.
Material and Methods
We have examined 27 patients with PHPT (24 women, 3 men; median age 55 years [37; 59]) within a year (12±1.3 months). All patients underwent biochemical and hormone evaluation before, in 3 daysand 1 year after surgical treatment for PHPT. The exclusion criteria were the glomerular filtration rate <75 ml/min/1.73 m², severe cardiovascular pathology, obesity, diabetes mellitus, using drugs affected calcium balance before and in 12 month after radical surgery. Control group was sex- and age-matched without cardiovascular pathology and any mineral disturbances (median serum calcium 2.45 mmol/l [2.42; 2.49], PTH 32.94 pg/ml [27.2; 41.6]).
Results
All patients initially had symptomatic PHPT (median serum calcium level 2.74 mmol/l [2.66; 2.9], PTH 123.8 pg/ml [85.8; 203]). Hypertensionwas observed in 37% and corrected with ACE-inhibitors or angiotensin II receptor blockers. PHPT patients had lower plasma renin activity (PRA) and higher serum angiotensin II (AT II) level comparing to control group (0.49 [0.11; 1.8] vs 1.23 [0.74;2.24] ng/ml*h, $P=0.02$ and 38 [30;42.2] vs 25.64 [20.14;35.44] pg/ml, $P=0.04$ respectively). At the 3rd day after surgery the blood evaluation revealed a significant decrease in PRA ($P=0.001$), whereas at 12th month there were decrease in AT II ($P=0.03$) and increase in PRA ($P=0.018$). Serum aldosterone level did not show any significant changes ($P=0.62$). There were no differences in the RAAS components between PHPT and control groups. However wefound a positive correlation of intact PTH with aldosterone in 3 days ($P=0.04$) as well as intact PTH with AT II levels at 12th month ($P=0.03$) after parathyroidectomy in non-therapy subgroup.
Conclusion
Our resultsdemonstrated the interaction between RAAS activity and PHPT, but further studies are required.
*The impact of impaired calcium-phosphorus metabolism on the renin-angiotensin-aldosterone system in patients with primary hyperparathyroidism. Mokrysheva N, Dobreva E, Bibik E, Eremkina A *Endocrine Abstracts* (2019) Vol 63. DOI: 10.1530/endoabs.63.GP24

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AEP214

Gene expression of claudins in NCKX3 knockout mouse

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Potassium-dependent sodium/calcium exchanger (*NCKX3*) is expressed in the brain, smooth muscle, the uterus, and intestine. NCKX3 gene plays a role in transporting intracellular calcium and potassium ions across the cell membrane in exchange for extracellular sodium ions. This gene is also associated with calcium metabolism in bones. Tight junctions have functional barriers for material transport and osmotic balance, which are regulated by calcium metabolism. Claudin, one of the tight junction protein members, take a part in a barrier preventing free diffusion and generate the paracellular pore pathway with unique cation- or anion-selectivity. The study has investigated the expressions of intestinal epithelial claudin genes in the duodenum of 6 week-aged Nckx3 knockout (KO) mice. The mRNA and protein levels of claudin-2, -5, and -15 were increased in Nckx3 KO mice compared to wild-type mice. However, mRNA and protein levels of claudin-12 were decreased in Nckx3 KO mice. We also found that *Ifit1, Zbp1, Oasl1, Oasl2, H2-DMb1* and *H2-Aa* genes were up-regulated in Ncxk3 KO mice, and *Gkn2, Gkn3, Tff2* and *Tff1* genes were down-regulated in Ncxk3 KO mice in gene expression profiles using an Affymetrix GeneChips. These results suggest that the *NCKX3* gene may be involved in tight junction and calcium metabolism in duodenum.

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AEP215

Progression of vertebral fractures in long-term controlled acromegaly: A 9-year follow-up study

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Objective
Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) excess results in both reversible and irreversible damage to the skeleton, and includes increased vertebral fracture (VF) risk in the presence of normal BMD. The prevalence of VFs is approximately 60% in controlled acromegaly patients, and these VFs can progress during short-term follow-up. We aimed to identify the course of VFs and their associated risk factors in a cohort of acromegaly patients in long-term remission during long-term follow-up.
Methods
Thirty-one patients with acromegaly (49% female, median age 60 yrs (IQR 53 – 66)), who were in biochemical disease remission for a median of 12 years (IQR 7 – 17) following uni- or multimodality treatment, were included in this longitudinal, prospective, follow-up study. Spine radiographs of vertebrae Th4 to L4 were assessed for VFs using the Genant score, at baseline, after 2.6 yrs and 9.1 yrs of follow-up. Progression was defined as either a new fracture, or a ≥1-point increase in the Genant score.
Results
The prevalence of VF at the baseline visit was 87.1% (27/31 patients), and the number of VFs was associated with active disease duration ($r=0.462$, $P=0.009$). Progression of VFs was observed in eleven patients (35.5%),

during the 9.1-year follow-up period, with a total incidence rate of 65.5 per 1,000 PY (Males 59.8/1,000 PY vs females 71.6/1,000 PY). VF progression occurred more frequently between baseline and the first follow-up visit, with an incidence rate of 86.9/1,000 PY, compared to the period between the first and second follow-up visit (incidence rate of 57.7/1,000 PY). Patients treated with surgery or radiotherapy had a higher risk of VF progression in this cohort in comparison with medical treatment (OR 17.3 (95% CI 1.5 – 203.7), $P=0.023$).
Conclusions
In this cohort of long-term well-controlled acromegalic patients, the prevalence and progression of VFs was high, showing that deleterious effects of the transient GH and IGF-1 excess persist despite achievement of long-standing remission. Therefore, there is a clinical unmet need for strategies to prevent fractures in newly diagnosed and chronic patients with acromegaly.

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AEP216

Assessment of physical fitness after bariatric surgery and its association with protein intake and type of cholecalciferol supplementation

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Background
Several studies showed that there is a relationship between vitamin and mineral status and muscle strength. In particular this is the case for handgrip strength (HS) and vitamin D deficiency. In bariatric surgery there is a risk of decrease in muscle strength after surgery and also vitamin and mineral deficiencies are not uncommon. The aim of this study is to assess the effect of low vitamin 25 (OH) cholecalciferol levels, high dose cholecalciferol supplementation regime and protein intake on physical fitness, measured using handgrip strength (HS) and the shuttle walk run test (SWRT).
Methods
For this retrospective study, 100 patients who have had bariatric surgery were included. Group A ($n=50$) used 800 IU oral cholecalciferol per day. Group B ($n=50$) used 800IU oral cholecalciferol daily and 50000 IU liquid colecalciferol monthly lifelong. Both groups were matched on common variables. To measure physical fitness we used the HS manometer of Jamar and the Shuttle Walk Run Test (SWRT) to assess physical capacity.
Results
No significant differences in HS and SWRT outcomes were found between patients with serum 25 (OH) cholecalciferol <75 nmol/l or >75 nmol/l. The postoperative HS is significantly influenced by protein intake ($P=0.017$) and no significant influence was seen in outcomes of the SWRT ($P=0.447$).
Conclusion
We have found that serum 25 (OH) cholecalciferol and different cholecalciferol supplementation regimes do not have a significant effect on HS and SWRT before, three and 6 months after surgery. It seems that protein intake plays a more important role in maintaining adequate muscle strength.

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AEP217

The Burden of chronic hypoparathyroidism in canada: A retrospective study using the institute for clinical evaluative sciences (ices) database

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Hypoparathyroidism is a rare disorder characterised by hypocalcaemia and hyperphosphataemia in the presence of low or inappropriately normal parathyroid hormone levels. Currently there are limited data on the burden of illness and healthcare resource utilisation (HCRU) associated with chronic hypoparathyroidism in Canada. A retrospective cohort analysis with matched controls was conducted to examine HCRU in patients with chronic hypoparathyroidism in Ontario, Canada. Data were extracted from the ICES database, which includes 7 integrated sources of clinical information. Patient selection included the following 3 stepwise criteria for hypoparathyroidism: (1) Hypoparathyroidism diagnosis based on 5 hypoparathyroidism diagnosis codes, (2) inferred hypoparathyroidism based on ≥1 procedure associated with the development of hypoparathyroidism in combination with a Ca^{2+} metabolism disorder, and (3) inferred hypoparathyroidism in the presence of disorders associated with hypoparathyroidism in combination with a Ca^{2+} metabolism disorderaccompanied by a diagnosis of hypoparathyroidism or a recognised complication of hypoparathyroidism in the following 6–24 months. Patients' baseline characteristics were assessed during a 1-year preindex period and were followed for up to 5 years after their index date, which was the date of the first diagnosis. Each patient was matched with 4 nonhypoparathyroidism controls based on age, sex, the Charlson Comorbidity Index, and hospitalisation (within ± 30 days of index date), and HCRU was compared using the Fisher exact test. The analysis included 427 patients with chronic hypoparathyroidism (mean age, 61 years; 75% female). Over the 5-year follow-up period, HCRU was significantly higher in patients with chronic hypoparathyroidism compared with the control cohort (Table). HCRU included visits to family physician/specialist, emergency department visits, same-day surgery, and hospitalisations. Patients with hypoparathyroidism had approximately 3-times-longer hospital stays during the first year of follow-up and overall longer hospital stays during all 5 years than the control group. Given the lack of a specific diagnostic code for hypocalcaemia, a code for both hypo- and hypercalcaemic diagnoses was used with selection criteria aimed at identifying those with hypoparathyroidism. Also, there was a time lag between data collection and data analyses. This study confirms the demographic features of patients with chronic hypoparathyroidism in Canada are consistent with other countries. Chronic hypoparathyroidism is associated with a substantial healthcare burden in patients and also on the healthcare system.
Funding: Shire, a Takeda company.

Table HCRU of Patients With Hypoparathyroidism vs Matched Controls

	Hypoparathyroidism, %	Control, %	*P* Value
Visits to family physician	100	97	<0.05
Visits to specialist	100	93	<0.05
Emergency department visits	59	81	<0.05
Same day surgery	62	50	<0.05
Hospitalisations	72	54	<0.05

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EP218

Cinacalcet use in pregnancy for a case of multiple endocrine neoplasia (MEN) 1 - associated primary hyperparathyroidism

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Hypercalcaemia in pregnancy is associated with foetal (IUGR, miscarriage and preterm delivery), maternal (hypercalcaemic crisis, pre-eclampsia, and hyperemesis) and neonatal complications, with severity of hypercalcaemia correlating with the risk of complications. The true incidence of primary hyperparathyroidism in pregnancy is unknown.
A 32 year old lady (G6 P5) with known MEN 1 and associated primary hyperparathyroidism (peak calcium 3.30 mmol/l) presented to the antenatal endocrine clinic at 12 weeks gestation. Her adjusted calcium was 3.24 mmol/l. She was referred for parathyroidectomy at the local tertiary endocrine/ma-

ternity hospital as she was in her second trimester, but because of pre-existing psychological problems she failed to attend on multiple occasions and was lost to follow-up. She re-attended at 29 weeks gestation having been unable to tolerate an OGTT for GDM due to nausea. Having declined transfer, and with ongoing issues with nausea, hypercalcaemia and osmotic symptoms, and considering the high levels of calcium recorded in pregnancy, she was counselled about the use of Cinacalcet and commenced on 30 mg OD with a calcium of 2.90.The dose was titrated up to 30mg TDS slowly with a gradual decline in calcium to 2.77. At 37+1 labour was induced due to IUGR and SGA. The following day a baby (2400 g) was delivered by NVD, with Apgar 10 and 10. Discharge was 24 hours later with no complications, and there have been no issues with the baby to date. Mother was discharged home with Cinacalcet as she was not breastfeeding.
Second trimester parathyroidectomy for primary hyperparathyroidism in experienced hands is the consensus recommendation for pregnancy. Cinacalcet is a calcimimetic drug, lowering PTH levels via the CaSR receptor, that is licensed in Europe for the treatment of primary hyperparathyroidism where surgery is not an option. Studies have efficacy in calcium lowering has been shown in primary hyperparathyroidism and also specifically MEN 1 related. A lack of clinical data means that it is not licensed for use in pregnancy, with current evidence limited to case reports. Animal studies have shown no concerns to date.
MEN 1 associated hyperparathyroidism in pregnancy brings its own challenges including genetic counselling and the question of extent of surgical intervention. To our knowledge this is only the second reported case of the use of cinacalcet for MEN 1 – related primary hyperparathyroidism in pregnancy and adds to the evidence base, though in this case efficacy was only mild.

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AEP219

An enlarged parathyroid gland emerging in the bed of the thyroid may mimic local recurrence in patients after total thyroidectomy for the papillary thyroid cancer: How does recovery from postsurgical hypoparathyroidism work?

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Anatomical proximity, common blood supply and variability of location of the parathyroid glands make them prone to damage in the course of thyroid gland surgery. Total thyroidectomy (TT) poses a greater risk of postsurgical hypoparathyroidism (hypoPT) than a unilateral lobectomy, and neck lymph nodes dissection is an established risk factor of HypoPT. HypoPT lasting longer than 6–12 months postoperatively is considered permanent. The mechanism responsible for the recovery of parathyroid gland function has been a subject of debate.
We present two patients in whom a neck sonography showed a hypoechogenic, vascularized structure in the bed of the thyroid gland which had been removed for papillary thyroid cancer (PTC).
A hypoechogenic lesion was visualized in the bed of the right thyroid lobe two years after TT for PTC of the ipsilateral thyroid lobe in a 70 yr man. Epithelial cells with signs of atypia, scattered lymphocytes as well as microcalcifications, suspicious for cancer recurrence, were found on fine needle biopsy. Excision of the lesion was performed. On the pathologic examination parathyroid adenoma, composed of main, oxyphyllic and clear cells was found. The patient was normocalcemic before as well as after the operation. Hypophosphatemia had been the only biochemical feature of hyperparathyroidism.
A 51-yr woman underwent TT for bifocal PTC. Parathyroid glands were not found in the pathological material, however she required treatment for postsurgical hypoPT. In the eighth year of the follow-up a raise in serum calcium concentration made further treatment for HypoPT unnecessary. Meanwhile a hypoechogenic vascularized 10 mm structure in the bed of the left thyroid lobe was shown on the sonography. Serum concentration of PTH, total calcium and phosphate were: 56 pg/ml (n 12–65 pg/ml), 2.4 mmol/l (n 2.2–2.65 mmol/l), 0.96 mmol/l (n 0.81–1.45 mmol/l), respectively. Scintigraphy with 99mTc-MIBI using planar and SPECT/CT technique was performed to elucidate a character of the lesion. A hot spot situated on the left and 15 mm beneath the thyroid cartilage, corresponding to the enlarged parathyroid gland was visualized.
According to the Guidelines for Treatment of Chronic hypoPT in Adults released recently by ESE, serum calcium concentration should be maintained in the low or slightly below normal range in order to avoid hypercalciuria.
In cases of postsurgical hypoPT, keeping low serum calcium concentration may favor hypertrophy or hyperplasia of the remaining functioning parathyroid parenchyma, which especially in patients with neck cancer anamnesis needs to be differentiated form a malignancy.

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AEP220

Fahr's disease in primary hypoparathyroidism – a case report

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Introduction
Basal ganglia calcification or Fahr's Syndrome is a rare form of neurological disorder. Its prevalence goes from 2 to 12.5 %. It can be primary (idiopathic) or secondary (from metabolic disorders especially from hypoparathyroidism).We present the case of a female patient with hypoparathyroidism and secondary Fahr's Disease.
Case description
The patient L.J. 61 years old, from Pogradec, Albania, who came to the emergency room with complaints of body weakness, severe fatigue, left side numbness and headache. The patient mentioned several similar episodes during the years. A month ago, she got a head injury, with an open bleeding wound because of disorientation and extreme fatigue. The patient was being treated only for Arterial Hypertension withIrbesartan/ Amlodipin (150/5), one tablet a day.
At the emergency room, a CT of the head was performed in order to exclude acute cerebral damages. During the examination, diffuse cerebral and cerebellar calcifications were seen, identified as FAHR Disease. The patient was first hospitalised in the Neurology Department where she was treated for her immediate symptoms. During her hospital stay her blood test came as shown below: Biochemical parameters within normal range. Thyroid stimulating hormone (TSH) 3.241 U/ml (0.4 – 4). Total calcium 3.3 mg / dl (8.6 – 10.2 mg/dl). Phosphatemia 7.6 mg / dl (2.5 – 4.5 mg/dl). Blood Magnesium level 1.7. mg / dl (1.8 – 2.2 mg/dl). Calcium in 24-hour Urine 8.7 mg / day (100 – 300 mg/day). Phosphorous in 24-hour urine 14.2 mg/dl (400 – 1300). Parathyroid hormone (PTH) 1.2 ng / L (15 – 65 ng/ L). 25 – OH – Vitamin D 15.24 ng/ml (> 30 ng/ml).
During the thyroid ultrasound, it was evident a heterogeneous bilateral structure favouring Hashimoto's thyroiditis.
Normal electroencephalogram was obtained. The patient was later transferred in our Department because of the new found diagnosis: Primary Hypoparathyroidism, FAHR Disease and Hypovitaminosis D.
Patient began treatment with intravenous Calcium and in just a few days her symptoms became less evident. She was discharged from hospital with oral Calcium (2000 mg/day) and Vitamin D3 (2000 UI/day) and was advised to check in with her endocrinologist for future follow up.
Conclusions
Fahr's Disease is a well-known but rare complication of hypoparathyroidism. In order to early diagnose,a thorough clinical-radiological and biochemical evaluation should be made.

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AEP221

Varied clinical presentation of pseudohypoparathyroidism- series of three distinctive cases

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Introduction
Pseudohypoparathyroidism (PHP) is a state of parathyroid hormone resistance and is characterised by low serum calciumand elevated serum phosphate and parathyroid hormone level

Case descriptions
We describe three cases diagnosed with PHP. *Case 1*: 14 year old male, known case of hypothyroidism, presented with carpopedal spasm and on treatment with 75 mg oflevothyroxine, with short height of 143 cm (less than 3rd percentile), BMI 23.23 kg/m^2 which was deemed to be overweight as per Indian Academy of Pediatrics (IAP) standard. The patient had signs of Albright Hereditary Osteodystrophy (AHO). Investigations revealed hypocalcemia (serum calcium 6.2 mg/dl), hyperphosphatemia (serum phosphorus level of 6.5 mg/dl) and high levels of Parathyroid Hormone (PTH) (889 pg/ml), normal vitamin D levels (25 OHD – 63.2 ng/ml). Alkaline Phosphatase (AP) levels were normal. TSH, FSH and calcitonin levels were elevated, with Sexual Maturity Rating (SMR) Tanner III and low testicular volume of 5 ml. *Case 2*: 13 years female presented with carpopedal spasm with signs of AHO, with short height of 128 cm (less than 3rd percentile), BMI 22.89 kg/m^2 (overweight). Investigations revealed hypocalcemia (serum calcium 5.8 mg/dl), hyperphosphatemia (serum phosphorus level of 4.8 mg/dl) and high levels of PTH (221 pg/ml), normal vitamin D levels (25 OHD –70.1 ng/ml), with elevated AP levels. TSH levels were normal. Patient had primary amenorrhea, hence had not attained menarche. FSH levels were 2.1 mIU/ml, LH 0.97 IU/l E 22 pg/ml. *Case 3*: 11 year old male presented with carpopedal spasm and convulsions. Investigations revealed hypocalcemia (serum calcium 7.3 mg/dl), hyperphosphatemia (serum phosphorus level of 7.56 mg/dl) and very high levels of PTH (1879 pg/ml), with normal AP. No signs of AHO, normal height, SMR was prepubertal with normal TSH levels.
Discussion
We diagnosed these as PHP based on the current global consensus statement with PTH resistance for the association of hypocalcaemia, hyperphosphataemia and elevated PTH in absence of vitamin D deficiency with normal magnesium levels and renal function. The case 1 with possible G(s) protein resistance, as FSH, TSH and calcitonin were high was diagnosed as PHP 1a. The second case was categorized PHP 1b but PHP 1a cannot be ruled out. Further, molecular analysis would have assisted with a precise diagnosis. The third case was diagnosed as PHP type 2. The management plan was based on true hypoparathyroidism including Vitamin D supplementation, with varied prognosis

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AEP222

Testosterone, estradiol and 25-hydroxyvitamin D effects at the proximal femur in 3D analysis from a standard 2D DXA scans of adult men

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Sex steroid hormones play a pleomorphic role in preservation of BMD. The BMD, the blood circulating 25-hydroxyvitamin D [25(OH)D], testosterone and estradiol levels may decline with age and to contribute to bone fragility. Low vitamin D is associated with increased falls number and fractures.
Recently, a new software solution, 3D-SHAPER - allows measurements of both trabecular and cortical bone as well as 3D images -, it incorporates a model-based algorithm to analyse the bone in 3D from a standard DXA scan, with no additional radiation to the patients.
However, the role of the blood steroid hormones on the 3D analysis of the proximal femur is not yet recognized.
Objectives
To correlate the 3D parameters analysis, as assessed by 3D-SHAPER, with blood steroid hormone levels of adult men.
Material and methods
All participants (adult men=97) had a DXA exploration (QDR4500 Acclaim and Discovery W, Hologic Inc, USA) at spine and at non-dominant femur (g/cm^2). 3D DXA modeling was performed using a software algorithm (3D-SHAPER v2.9, Galgo Medical, Spain) in order to derive QCT-like subject-specific 3D models from the hip DXA scans of the study subjects. The following 3D measurements were extracted: the trabecular and cortical volumetric BMD (Trabecular/cortical vBMD), the cortical thickness (Cth) and the cortical surface BMD (Cortical sBMD) as well as neck cross-sectional moment of inertia (CSMI) and Z modulus. In addition, appendicular fat and lean mass were assessed using dedicated DXA acquisition.
Blood was collected for 25(OH)D (ng/ml), total testosterone (T, ng/ml), 17β-estradiol(E_2, pg/dl) and sex hormone binding globulin (SHBG, nmol/ml) measurements.
Adequate statistical tests were used.
Results
In 97 adult men [mean (± SD) age 60.1(±13.5) years, mean BMI 25.3 (2.7)kg/m^2] the mean BMD at the lumbar spine BMD=1.030 (± 0.2) and at the total femur=0.978 (±0.1), total body fat mass=20.7 (±15.7) kg and total body lean mass=52.8 (±15.5)kg. The mean E_2=28.3 (±19.6), T=4.9 (±11.8), SHBG=43.2 (±19.2) and 25(OH)D=24.1 (±11.0). The some of correlation coefficients are in Table below. No correlations were detected for the 3D parameters and 25(OH)D and the E_2 levels.

3D Analysis vs	vBMD Integral Total mg/cm^3	*P*	Volume Integral Total cm^3	*P*
T	–0.3035	0.0056	0.2499	0.0296
SHBG	0.2491	0.0223	0.2175	0.0469

Conclusions
It seems that androgens play a very important role on bone strength; normal men with low blood testosterone levels may have low 3D parameters and thus worse bone strength; it is possible that testosterone acts positively in bone strength. Further studies are needed on a larger cohort and it might be worth to investigate men with hypogonadism.

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AEP223

Trabecular bone score assessment in heart transplant recipients stratified by time after transplantation

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Objective
Bone strength post heart transplant (HT) is affected by many factors including glucocorticoids, calcineurin inhibitors, hypogonadism, vitamin D deficiency, secondary hyperparathyroidism and cachexia. Trabecular bone score (TBS), novel texture index derived from lumbar spinal DXA improves fracture risk assessment in several different high-risk populations, whereas it remains largely understudied in HT recipients. We aimed to evaluate factors that affect TBS after HT.
Materials and Methods
We conducted cross sectional cohort study including 87 HT patients (69 males and 18 females),of median age 59.3 years (IQR 53–66.5) that were stratified according to post-transplantation time into Group 1 (less than 1 year after HT;22 patients), Group 2(1 to 3 years post HT; 15 patients) Group 3 (3 to 5 years post HT; 31 patients) andGroup 4(more than 5 years post HT; 19 patients). We compared TBS and BMD among those groups. In addition, we assessed impact of methylprednisolone, bisphosphonate, male hypogonadism and presence of vertebral fractures on TBS.
Results
Compared with Group 1, patients in the 2nd and 3rd Group had lower TBS (1.35 (IQR 1.26–1.41) vs 1.30 (IQR 1.26–1.36) vs 1.25 (IQR 1.17–1.29) respectively; (pairwise comparison between Group 1 and 3 P=0.020)), whereas in Group 4 TBS was higher than in Group 3 and comparable to Group 2 (1.31 (IQR 1.23–1.38). By contrast, BMD and T values did not differ among the 4 groups. Body mass index (BMI) was significantly higher in each group along observed time period (Group 1 (22.6 kg/m^2 (IQR 21.1–24.4)) vs Group 2 (24.7 kg/m^2 (IQR 24.2–28.0) vs Group 3 (28 kg/m^2 (IQR 25.5–30.4)) vs Group 4 (27.6 kg/m^2 (IQR26.2–30.0); <0.001 pairwise comparison: Group 3 vs Group 1 P <0.001 and Group 4 vs Group 1 P <0.001). Methylprednisolone, bisphosphonates, presence of male hypogonadism and vertebral fractures had no impact on TBS.

Conclusions
TBS in HT patients significantly differed among groups stratified by time after transplantation, independently of treatment with methylprednisolone, bisphosphonates or presence of male hypogonadism and vertebral fractures. By contrast, BMD was comparable among all Groups over time, being considered as less sensitive indicator of bone strength over post-transplantation time. Spontaneous reversal of declining trend in TBS observed more than 5 years after transplantation along with gradual significant improvement in BMI, imply cardiac cachexia and its reversal as one of the potential impacts on bone microstructure. The role of TBSin this population needs further investigation in longitudinal studies.

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AEP224

Efficacy of teriparatid therapy in resistant hypocalcemia depending postoperative hypoparathyroidism

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Objective
While postoperative hypoparathyroidism can usually be controlled with elemental calcium (Ca) and calcitriol therapy, rarely this treatment may be inadequate and teriparatid therapy may be used as an alternative. In the literature, it is reported that teriparatid therapy is effective and reliable in the treatment of patients with postoperative hypoparathyroidism, as well as improving quality of life and reducing the frequency of hospitalization. In this report, we present a case of postoperative hypoparathyroid disease that was followed up due to treatment resistant hypocalcemia and responded to teriparatid therapy.
Case
41 - year-old female patient, 3 years ago due to papillary thyroid carcinoma after total thyroidectomy developed in the hands-feet with numbness and tingling complaints were admitted to the outpatient clinic. Serum total calcium: 4.9 mg/dl, phosphate:5.5 mg/dl, intact PTH:0.7 ng/l were determined and oral Ca and calcitriol treatment was started after the diagnosis of postoperative hypoparathyroidism. Although calcitriol was given 6 mg/day, elemental Ca 15 gr/day dose, Ca values remained at 6.5–7 mg/dl (Table 1) level after the patient received replacement therapy for approximately 2 months. The patient's complaints continued clinically and the patient was hospitalized several times due to the need for intravenous Ca. Subcutaneous teriparatide acetate (recombinant human parathyroid hormone 1–34) was administered once a day at a dose of 20 µg/80 µl in addition to the existing treatment of the patient who did not respond to the treatment. Calcitriol requirement decreased to 2 mg/day and elemental Ca requirement decreased to 6 g/day according to Ca follow-up after Teriparatid treatment. After treatment, the patient's total serum Ca value increased to 8.2 mg/dl and the patient's hypocalcemia symptoms improved.

Table 1 Laboratory values before and after teriparatid treatment of the patient.

Laboratory parameters / Normal value range	Postoperative basal values	After initial dose of Ca and Calcitriol	After maximum dose of Ca and Calcitriol	After teriqaratid therapy
Serum total calcium (8.7 – 10.4 mg/dl)	4.99	6.84	7	8.2
Serum phosphate (2.4 – 5.1 m g/d l)	5.56	5.78	4.48	4.5
Serum intact PTH (18.4 – 80.1 ng/l)	0.7	4,9	4.6	5.8
25-0H Vitamin D (25 – 80 ng/m l)	45.6	31.8	31.6	205
Serum alkaline phosp hate (53 – 128 U/l)	56	52	37	52
Serum albmin (32 – 48 g/l)	42.7	38.8	37.7	38
Serum magnesium (1.3 – 2.7 mg/d l)	1.64	1.89	1.73	1.68
24 hr urine calcium (100–300 mg/day)	211.9	–	202	–
24 hr urine phosphate (0.4–1.3 mg/day)	0.542	–	0.297	–

Conclusion
It should be noted that recombinant human teriparatid therapy may be effective in patients with postoperative hypoparathyroid disease, which requires intravenous calcium infusion and hospitalization despite high doses of calcium and calcitriol therapy, and treatment change should not be delayed.

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AEP225

Trabecular bone score in postmenopausal women with primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism (PHPT) is generally associated with increased fracture risk at all skeletal sites although greater bone loss is observed at the cortical than the trabecular bone sites. AsBMD alone does not adequately predict fracture risk, trabecular bone score (TBS) is proposed as a new method supporting risk assessment.
The aim of this study was to investigate correlation between TBS andthe severity of primary hyperparathyroidism.
Methods
The study group consisted of 29 postmenopausal women (age 64.6±8.2 years) with PHPT. Seven patients were diagnosed with kidney stones, two had bone fracturesand 1 had recurrent pancreatitis. In all patients BMD was measured by DXA at the lumbar spine (LS), the femur neck (FN), the distal third of the radius(R1/3) and the distal tenth of the radius (RUD). TBS was measured in LS –BMD. The correlation between TBS, BMD, laboratory results and clinical symptoms of PHPT were evaluated.
Results
BMD mean values (T-score) for LS, FN, R1/3 and RUD were –2.5±1.4, –1,7±0.6, –3.1±1.4, –2.4±1.07, respectively. TBS mean value was 1.1±0.12 (T-score – (–) 3.2±1.4) which means high risk of fractures. Serum parathormone concentration was 206±191 ng/l, serum calcium concentration 11.3±1.2 mg/dl and serum phosphate concentration was 2.5±0.2 mg/dl. There was no correlation between TBS and biochemical parameters such as: PTH, calcium, phosphate and 25-OH-Vitamin D, alkaline phosphatase, serum creatinine concentration andurine calcium excretion. The only correlation found was positive correlation between TBS and BMD at the ultradistal radius region (Spearman's $R=0.48$, $P<0.05$). We did not observe any correlation between TBS andtime since menopause or time since diagnosis of hyperparathyroidism. Body weight and BMI exerted a negative effect on TBS ($R=-0.54$ and $R=-0.38$ respectively, $P<0.05$).
Conclusions
Our observations suggest that TBS is not strongly associated withthe severity of PHPT. However, TBS value in patients with PHPT is significantly decreased, hence to determine its role as a predictor of bone fractureit is necessary to conduct long-term studiesin larger groups, especially in patients with fractures.

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AEP226

The incidence of nephrolithiasis and osteoporosis in patients with asymptomatic hyperparathyroidism

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Introduction
The clinical profile of patients with primary hyperparathyroidism has changed significantly in the last decades considering the fact that most cases are asymptomatic. This could be attributed to early diagnosis due to routinely serum calcium measurement. Only 5–27% of patients present with symptoms or signs related to osteoporosis, nephrolithiasis and hypercalcaemia. However, in patients with asymptomatic primary hyperparathyroidism (APHP) data concerning the incidence of these disorders are sparse.
The aim of our study was to record the incidence of nephrolithiasis and osteoporosis in patients with APHP.
Patients and Methods
57 women, aged 62.8±13.3 years, with APHP and normal renal function (GFR >60 ml/min/1.73 m^2) were studied retrospectively. None of the patients was on treatment with bisphosphonates, denosumab, thiazide diuretics or calcium and vitamin D supplements. All were assessed with serum calcium (corrected for albumin), phosphorus, iPTH, 250HD3 and creatinine levels, twenty-four-hour urinary calcium and creatinine levels, while GFR was calculated. Kidney ultrasound and bone density measurement (BMD) with DEXA were performed. Osteoporosis was considered when T-score was less than –2.5 at any site (L2-L4, femur neck and distal radius).
Results
Twenty out of the 57 patients with APHP (35.0%) had nephrolithiasis and 25 (43.8%) had osteoporosis. Patients with nephrolithiasis vs those without, had higher 250HD3 (24.6±8.0 vs 17.1±7.7 ng/ml, $P<0.003$), while there was no difference in age, BMI, serum calcium and PTH levels, and twenty-four-hour urinary calcium excretion ($P>0.05$). Patients with osteoporosis were older (69.3 ±10.0 vs 57.4± 13.1 years, $P<0.001$) and had higher serum PTH levels (160.6±93.9 vs 101.3±21.5 pg/ml, $P=0.002$), but did not differ in other parameters from women without osteoporosis.
Conclusions
Nephrolithiasis and osteoporosis are common in patients with asymptomatic primary hyperparathyroidism and therefore, bone mass density evaluation and kidney ultrasound should be included in the initial work up for early diagnosis and management.

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AEP227

Osteogenesis imperfecta type V due to a rare mutation c.119C> T in the IFITM5: A case report

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Osteogenesis imperfecta (OI) is a heritable skeletal disorder caused by defective bone formation. OI type V (MIM#:614757) develops due to mutation in the *IFITM*. Mutation c.-14C >T in the *IFITM5* is more common whereas only five reported patientshave a c.119C >T mutation. Patients with *IFITM5*:c.119C >T mutation usually have low-traumatic fractures in the prenatal period of development, severe limb and chest deformities, short height, vertebral fractures and inability to move independently in a childhood.
We present acase of an adult patient with OI type V due to a rare mutation p.119C>T:p.S40L in the *IFITM5*. A 32-year-old female (height, 95 cm; weight, 30 kg) was hospitalized with back pain, pain in joints and limited ability to move in a wheelchair. She had severe chest and long bonesdeformities, and joints contracture. CT scan showed the presence of ossifications of the interosseous membrane between the ulna and radius; multiple vertebral fractures. The patient denied relatives with similar clinical features, she did not have hearing loss, blue sclerae ordentinogenesis imperfecta. The patient sufferedher first fractureat the prenatal period of development. During childhood she had numerous fractures: long lower and upper limb bones, ribs, clavicle. At the age of 7 she had osteosynthesis on both femurs and tibiae. She became immobile at the age of 13.The patient followed treatment with zoledronic acid, calcium and vitamin D supplements from 26 to 28 years of age and then teriparatide 20 mg/day. The last fracture was diagnosed at the age of 29. Serum calcium, phosphate, creatinine, vitamin D, C-terminal telopeptide of type I collagen, PTH were within the reference ranges, but osteocalcin was slightly elevated 47.42 ng/ml (11–43).
Conclusion
This is a case of sever OI type V surviving into adulthood. OI is a clinically and genetically heterogeneous disease, so testing of pathogenic variants of the *IFITM5* may be useful.

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AEP228

A case of severe asymptomatic hypercalcaemia in IgG kappa multiple myeloma, focal bone disease and inappropriately normal PTH as a differential diagnostic dilemma

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We present the case of 63 years old female patient who was diagnosed with IG G kappa multiple myeloma in 2007. Cytogenetics investigations revealed high risk for progression of the disease (cytogenetics: 17 p deletion and t (4/14). The patient decided against active treatment. Over 10 years she was kept under observation with no symptoms. Her basal paraprotein levels slowly progressed from 14 g/l up to 18 g/l. In 2017 she developed mild hypercalcaemia (corrected calcium 2.72 mmol/l) and imaging investigations revealed focal myeloma bone deposits with no activity on FDG PET scan. During the following two years the patient remained asymptomatic. Calcium levels continued to rise (peak corrected calcium up to 3.2 mmol/l) despite treatment with bisphosphonate infusion (4 mg Zoledronic acid). Paraprotein levels increased up to 43 g/l. Inappropriately normal PTH levels, prompted further investigations in order to exclude concomitant hyperparathyroidism. Bone density scan revealed normal bone mass, bone markers showed normal metabolic bone activity (CTX 0.37, PNP1 58). Imaging investigations showed no topical parathyroid disease. We considered the differential diagnosis of pseudo-hypercalcaemia related to high levels of abnormal paraproteins. A simple venous blood gas test revealed normal ionised calcium of 1.20 (NR <1.3) which supported the hypothesis. Subsequent drop in PTH levels down to 2.8 pmol/l (NR >1.6) is likely to represent a response to variation in serum calcium levels within the reference range. Multiple myeloma bone disease in 90% of patients presents with symptomatic osteolytic bone disease. Treatment with bisphosphonates is essential to suppress cytokine induced activation of RANKL/OPG system and to correct hypercalcaemia. Disease control remains the major element in treatment of myeloma bone disease. Simple biochemical markers could support clinicians in their differential diagnostic reasonings and guide further therapeutic management. Pseudo-hypercalcaemia due to high paraprotein levels should be considered in the differential diagnosis of hypercalcaemia in multiple myeloma in asymptomatic patients to avoid unnecessary investigations and interventions.

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AEP229

Trabecular bone score in subjects after simultaneous pancreas kidney transplantation

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Introduction
Osteoporosis is a well known long-term complication after simultaneous pancreas kidney transplantation (SPK). Alterations of bone microstructure contribute to the risk of fracture and trabecular bone score (TBS) measurement offers and additional tool to quantify bone microarchitecture impairment.

Methods
There were 33 subjects with type 1 diabetes mellitus (23 men, 10 women, mean age 43.4±9.8 years) participating in a prospective observational study with areal bone mineral density (aBMD) of lumbar spine (LS) and femoral neck (FN) and lumbar TBS evaluation in years 0, 1 and 3 after the successful SPK. Apparatus Lunar Prodigy Primo with TBS insight software version 3.0.3.0 was used for the data retrievement.
Results
Mean creatinine, HbA1c (IFCC) andPTH concentrations 3 years after SPK were as follows: 136.7±68.9 umol/l; 38.8±6.9 mmol/mol and 11.7±8.1 pmol/l. LSaBMD wasinitially in osteopenic range but increased significantlyduring the whole follow-up (Z-score: –1.12±1.31 vs –0.14±1.25; $P<0.001$), FN aBMD remained diminished with only insignificant increase (Z score: –1.42±0.92 vs –1.19±0.83; NS). Mean TBS was low (1.201±0.118) and high-risk value (<1.23) was initially registered in 18 subjects (54%). Maximal TBS increment was documented during the first post-transplant year (1.201±0.118 vs 1.292±0,108; $P<0.01$) with later stabilization (1.292±0.108 vs 1.272±0.115; NS).
Conclusions
Subjects after SPK are at risk of low aBMD especially at cortical sites. Bone microstructure is significantly affected as documented by low TBS and diminished valuespersist despite its improvement during the first post-transplant year. Further investigation to identify risk factors connected with low TBS values and its role in fracture prediction in post-transplant period is needed.

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AEP230

Vertebral fractures in patients with castration-resistant prostate cancer undergoing treatment with Radium-223: A longitudinal study in the real-life clinical practice.

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Radium-223 was associated with high incidence of non-vertebral fractures in patients with castration-resistant prostate cancer (CRPC). The determinants of this effect are unknown and it is still unclear whether Radium-223 may induce skeletal fragility regardless of other therapies of CRPC. We aimed at evaluating the incidence and determinants of vertebral fractures (VFs), i.e. the hallmark of skeletal fragility, in CRCP patients undergoing Radium-223 therapy in the real-life clinical practice. We retrospectively reviewed 49 CRPC patients with symptomatic bone metastases treated with Radium-223 between July 2015 and May 2019. All patients underwent 11C-Choline PET/CT examination and VFs were assessed by the Genant's method using lateral images of spine CT and excluding from the analysis the vertebral bodies affected by bone metastases. Before starting Radium-223, 24 patients (49%) had VFs significantly associated with duration of androgen-deprivation therapy (ADT) (odds ratio: 1.29, C.I. 95% 1.01–1.64; $P=0.04$) and abiraterone acetate plus prednisone therapy (odds ratio 3.80, C.I. 95% 1.07–13.57; $P=0.04$). Patients received median number of 4 radium-223 doses (range 2-6) and were followed-up for a median period of 11 months (range 2–44). Radium-223 therapy achieved bone pain relief in 81.3% of patients, average PSA values reduction of 248±45%, progression free-survival and overall survival improvement, respectively in 41.7 % and 24.5% of patients. Forty-four patients were evaluated for incident VFs. During Radium-223 therapy, newVFs developedin 11 patients (25%) in relationship with pre-existing VFs (Hazard Ratio 6.89, C.I. 95% 1.17–40.59; $P=0.03$) and change in serum alkaline phosphatase values (Hazard Ratio 0.97, C.I. 95% 0.95–0.99; $P=0.02$), whereas the correlations with abiraterone plus prednisone therapy and duration of ADT were lost. Noteworthy, incident VFs did not correlate with the therapeutic outcomes of Radium-223. This observational study confirms that ADT may cause skeletal fragility especially when abiraterone is combined with prednisone. Interestingly, this study provides also aconvincing evidence that in real-life clinical practice, Radium-223 therapy may directly induce skeletal fragility with high risk of VFs independent of ADT and abiraterone plus prednisonetherapy. Therefore, skeletal health should be pro-actively evaluated in all patients with prostate cancer undergoing ADT and mainly in those candidate to Radium-223 therapy, in order to plan a therapeutic strategy for preventing fragility fractures in this clinical setting.

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AEP231

A follow-up of a patient with osteopetrosis successfully treated with bone marrow transplant at the age of 28

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Introduction
Osteopetrosis is a rare hereditary disease caused by defective osteoclast differentiation or function. Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for some forms of osteopetrosis. HSCT is usually performed in infancy. Currently there is also experience of HSCT for osteopetrosis in adults[1]. In this clinical case we describe the follow-up of a patient treated with HSCT[1] at the age of 28.
Clinical case
This male patient was diagnosed with osteopetrosis at the age of 5. He has one affected and one healthy sibling. His weight at birth was 4000 g and height 51 cm. He had a developmental delay (he learned to walk at the age of 3). A *CA2* mutation (Chr8:86389420 C>G p.Y193X) was revealed. Due to severe anemia and thrombocytopenia the patient required multiple blood transfusions. He also suffered from multiple low-traumatic fractures (clavicle, shoulder, multiple hip, tibia and fibula fractures). Secondary adrenal insufficiency was diagnosed due to extensive bone growth including sella turcica and the patient required hydrocortisone 10-15 mg per day. At the age of 26 his BMD was aboveaverage +6.0 SD Z-score lumber spine and+5.1 SD Z-score Total Hip. At the age of 28 the patient underwent HSCT[1]. He was re-examined in our clinic at the age of 30 with height 147.5 cm; weight – 54 kg with significant improvement in his clinical presentation: Hb – 123 g/l, thrombocytes – 134×10^9 cells/l ($152–372 \times 10^9$ cells/l), without any low-traumatic fractures, he did not require treatment for secondary adrenal insufficiency anymore: urinary free cortisol – 126,9 nmol/24 h; morning cortisol – 352 nmol/l. CT of the head revealed basal ganglia calcifications and thickening of the bones of the facial skeleton, temporal and sphenoid bones.
Conclusion
HSCT was beneficial, leading to the reversal of most dangerous osteopetrosis complications in an adult patient with moderate severity osteopetrosis.
Reference
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AEP232

Complex physical rehabilitation effect on postural control in patients with osteoporotic vertebral fractures

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Aim
To evaluate effect of complex physical rehabilitation on postural function in patients with osteoporotic vertebral fractures (VFs).
Materials and methods
Study comprised of 90 osteoporotic patients aged 50–80 (65.4±9.1 years) with VFs who were randomized as 2:1 into intervention group (group 1, $n=60$) and control group (group2, $n=30$). Patients in group1 received an intensive rehabilitation course including back muscle training with mechanical loads #10; sensorimotor training on double unstable platform #10; kinesohydrotherapy in a pool #15; physical exercises in a gym #10. Group 2 was prescribed only physical exercises in a gym #15. All patients were tested with Stabilometry, one leg standing test and Fukuda test at baseline,

at the end of rehabilitation course and in a month after the rehabilitation as follow-up.
Results
Baseline examination showed no any significant differences between groups in stabilometric parameters and coordination tests ($P>0.05$). There were significant changes in group1 after the rehabilitation course vs baseline in balance function coefficient (BFC) with opened eyes from 77.0±7.6 to 84.1±8.6% ($P=0.008$) and with closed eyes from 67.1±9.7 to 73.8±9.6% ($P=0.007$), at the area of statokinesiogram (ASKG) from 176.8±170.2 to 131.9±210,4 mm^2 ($P=0.04$), pressure center velocity (PCV) from 9.5±4.4 to 12.2±10.1 mm/s, ($P=0.0004$), displacement in Fukuda test from 41.4±21.3 to 32.8±14.5, ($P=0.03$) and in One leg standing test on both legs with open eyes from 9.7±21.7 to 17.8±31.8 sec and from 9.5±15.3 to 17.1±30.1 respectively ($P=0.001$). In group2 there was improvement in PCV from 9.2±4.7 to 10.1±3.9 mm/s ($P=0.05$). Positive dynamics in balance tests (BFC with open and closed eyes, PCV, ASKG, displacement in the Fukuda test, time for both legs in One leg standing test) were maintained in group1 in month of follow-up after the rehabilitation treatment. All the postural control parameters were significantly better in group 1 vs group 2 after 1 month of follow-up ($P<0.01$).
Conclusions
The complex physical rehabilitation aimed for trunk muscles and coordination trainings improve the postural function in patients with osteoporotic VFs.

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AEP233

Abstract withdrawn

AEP234

Brown tumor with multiple localizations in primary hyperparathyroidism: About a case

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Introduction
A brown tumor is a rare osteolytic non-neoplastic lesion, due to an anomaly of bone metabolism, occuring in primary, secondary or tertiary hyperparathyroidism.
This is a case about a brown tumor with multiple localizations seen in primary hyperparathyroidism.
Observation
A 42 year old patient,with a history of Behçet disease diagnosed at the age of 38, is hospitalized in our department for the management of a fortuitously diagnosed hypercalcemia at 3.11 mmom/l. The treatment consisted in a rehydration, resulting in the progressive decrease of hypercalcemia.
A primary hyperparathyroidism was diagnosed based on a hypercalcemia reaching 3.21 mmol/l, hypophosphatemia at 0.6 mmol/l, an elevated level of PTH at 2278 pg/ml (N : 15–72), a hypercalciuria at 11.8 mmol/24 h. A vitamin D deficiency at 8.1 mg/l was also diagnosed. A cervical ultrasound and a Sestamibi parathyroid scintigraphy were done concluding to a parathyroid adenoma localized in the right inferior pole. A study of the repercussions of the hyperparathyroidism has shown an osteoporosis, a medullary nephrocalcinosis and a right renal lithiasis.
A surgical indication was established, after a preoperative preparation by vitamine D and bisphosphonates. After the surgey, the patient developed a hungrybone syndrome, treated by a calcium and vitamin D supplementation. A month after that, the patient developed pain in both legs, leading to the discovery of multiple osteolytic images in the both tibias, on the radiography. A bones scintigraphy showed multiple pathological fixations in the skull, right clavicle, the sternum, rib cage, lower extremity of the left femur and the two tibias, all in favor of brown tumors. The patient refused to do a bone biopsy and was treated by bisphosphonates.
Discussion and conclusion
Brown tumors complicate 4.5 % of cases of primary hyperparathyroidism. They are the result of an important osteoclastic activity. The most common localizations are the ribs,clavicles, pelvicgirdle and the mandible. The localization in the long bones is rare. In the case of this patient, there are multiple localizations. These benign bone tumors pose a problem of differential diagnosis with osteolytic metastases. Biopsy, if realised, show multinucleated giant cells, but these latters are not specific

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AEP235

The transition range and acceleration from normocalcemia to hypercalcemia in patients with primary hyperparathyroidism: Does it provide a new perspective?

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Objective
Primary hyperparathyroidism (PHPT) is a clinical condition characterized by hypercalcemia-specific symptoms and signs caused by excessive secretion of parathormone. After the evaluation of blood calcium measurements within routine tests, the frequency of hyperparathyroidism increased and there is a marked decrease in the frequency of classical symptoms and signs. Recently, most PHPT cases are detected in the asymptomatic period, and which of these asymptomatic patients will go to surgery,is individually evaluated. In this study, it was investigated whether there is any feature that can be taken into account in the diagnosis and follow-up by considering the calcium course in the period until the development of hypercalcemia.
Methods
The biochemical records of patients who were operated with the diagnosis of PHPT and whose histopathological diagnosis was parathyroid adenoma were reviewed from our database. We evaluated patients who had at least 2 consequtive albumin corrected calcium levels before the time of first hypercalcemia were detected, during the preoperative period. The date when the first hypercalcemia detected, first hypercalcemic value, normocalcemic values and dates, and the intervals between them were recorded. We determined delta change and percentage changes within the patients who had at least 1 year of periyod between normocalcemia values.
Results
In this study,18(94.7%) female and 1(5.3%) male,19 patients with PHPT were included and the mean age was 52.21±10.9. The median time to develop hypercalcemia after the last normocalcemia time was 5 months (0.5–36 months). Median hypercalcemia level was 10.3 mg/dl (10.1–10.9),median for last normocalcemia was 9.8 mg/dl (9.3–10.0). It was found that the development time of hypercalcemia was decreasedas the normal calcium level increased ($P=0.044$). A higher hypercalcemic value was found as the time between normocalcemia and hypercalcemia increased ($P=0.049$). The course of increase in calcium levels over time was statistically significant ($P=0.0$). For the course of changes in normocalcemic values determined in these 19 patients until hypercalcemia was detected, delta change and percentage changes of 12 patients with 2 normocalcemic values at least 1 year intervals before the development of hypercalcemia were calculated.
Conclusion
Recently, some patients with primary hyperparathyroidism who are asymptomatic at the time of admission are treated surgically and some of them are followed up. Individualized treatment is applied in this regard, according to the guidelines some of the patients recommended surgery are followed, some of those recommended for follow-up are also operated. More information about the natural course of untreated primary hyperparathyroidism can help resolve this imprecise situation.

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AEP236

Role of preoperative calcium and vitamin d therapy to prevent postsurgical hypoparathyroidism

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Background
Postsurgical hypocalcemia is the most common and most troubling long-term consequence of thyroidectomy. In this study, we investigated the potential role of routine calcium or vitamin D supplementation in preventing postsurgical hypoparathyroidism.
Methods
We carried out a systematic search of MEDLINE and EMBASE for English-language publications using the keywords "calcium", "vitamin D", and "thyroid cancer". The primary outcome was any postoperative hypocalcemia, and the secondary outcome was symptomatic hypocalcemia. We analyzed data from the studies using Review Manager (RevMan, Version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).
Results
Four studies that included 381 patients were eligible for this meta-analysis. The random-effects model showed no significant difference in the occurrence of hypocalcemia between calcium/vitamin D treatment and placebo/no treatment (OR 0.82, 95% CI 0.36–1.86, $P=0.63$). The occurrence of symptomatic hypocalcemia was lower in patients with calcium/vitamin D treatment than in those with placebo/no treatment (OR 0.44, 95% CI 0.22–0.88, $P=0.02$). In combined results, we found that preoperative calcium and calcitriol supplementation, in addition to routine postsurgical supplementation, was associated with a reduced incidence of symptomatic hypocalcemia after total thyroidectomy.
Conclusion
This study supports the use of preoperative calcium and vitamin D supplementation in conjunction with routine postsurgical supplementation for patients undergoing total thyroidectomy.

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AEP237

Is BMD still useful when we have FRAX?

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Introduction
The FRAX fracture risk assessment algorithm is able to integrate clinical risk factors independent of bone mineral density (BMD), evaluating the 10-years probability of fracture, therefore identifying patients in need for antiosteoporotic treatment, in which case bypassing the WHO (World Health Organization) criteria for densitometric diagnosis of osteoporosis.
Material and methods
We retrospectively analysed a total of 91 scans of women aged between 65–75 years old, from authors' DXA (dual X-ray absorptiometry) database, with no other medical records. We divided the patients in 3 groups according to Romanian FRAX intervention threshold and fracture risk prediction: low-risk, intermediate risk and high risk of fracture. Using DXA scan with Lunar IDXA, we extracted bone composition parameters like spine and hip BMD expressed as T-score. We analysed the obtained data using IBM SPSS Statistics 20.
Results
A total of 91 scans of postmenopausal women (mean age 69.9±3.01) with no previous diagnosis of osteoporosis, nor previous antiosteoporotic treatment, were included in our study, from which 18 of them (19.8%) had spine or hip T-score consistent with osteoporosis diagnosis (T score≤–2.5 DS), 47 (51.64%) with osteopenia and 29 (31.86%) had normal osteodensitometric parameters. Based on the interpretation of the Romanian FRAX without BMD results, 15 patients, (16.48%) were considered to be in the high-risk group, therefore, eligible for treatment, 44 (48.35%), 1 in the intermediate risk group, needing hip BMD addition and 32 (35.16%) in the low-risk group, for witch non further inquiry wold be necessary. Regarding the fracture risk probability estimated by Romanian FRAX without BMD, In the low-risk group, 2 out of 32 women had densitometric osteoporosis, 19 had osteopenia and 11 had normal BMD; on the other hand, in the the FRAX high-risk group, 5 women had osteoporosis, 7 had osteopenia and 3 out of 15 had normal BMD.
Conclusions
Although FRAX nowadays is widely used, accessible and proved to be efficient screening tool, measuring the BMD still plays an important role for fracture risk prediction, in which case it's value can be increased by combining it with more clinical factors. Considering the limited number of patients, the need of a more precise personal medical history, we cannot cast doubt on the utility of FRAX for screening patients at high or low-risk of osteoporosis, but because here is no 100% overlap between FRAX and densitometric results, BMD remains the core concept in the osteoporosis diagnosis and treatment.

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AEP238

Osteoporotic bone fracture hiding a rare sex chromosome disorder: Case report

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Introduction
The XXYY Syndromeis an extremely rare sex chromosomal disorder characterized by the presence of extra X and Y chromosomes, and clinically by tall stature, dysfunctional testes associated with infertility and hypogonadism, cognitive, affective and social functioning impairments, global developmental delay, and an increased risk of congenital malformations.
Case Report
A 46-year-old man was referred to theFracture Osteoporosis OutpatientClinic after a osteoporoticleft hip fracture.
He had a previous osteoporotic right hip fractureat 43 years-old and epilepsy, hypothyroidism, esophagitis, dyslipidemia and cognitive deficit.
Central obesity, reduced facial and body hair, poor muscle development, gynecomastia and testicular atrophy were observed.
The analytical evaluation showed normal thyroid function, P1NP 70.8 ng/ml, 25(OH)D 18.1 ng/ml, FSH18.7 U/l, LH 14.8 U/l,total testosterone 46.6 ng/dl. A karyotype study revealed a 48, XXYY syndrome.
He was started on intravenous zoledronic acid, intramuscular testosterone and oral calcium and vitamin D supplementation.
Conclusion
The 48 XXYY Syndrome,previously considered as a variant of Klinefelter syndrome, is nowadays described as a distinct clinical and genetic entity, as the medical problems and more complex psychological and neurodevelopmental involvement are usually present. The hypogonadism may also predispose these patients to osteoporosis and fragility fractures.

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AEP239

The assessment of risk factors for osteoporosis and probability of osteoporotic fractures in patients undergoing medical rehabilitation

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The aim of the study was to evaluate the risk of osteoporosis and related fractures in the patients treating in in-patient rehabilitation department.
Methods
The survey was conducted by means of questionnaire of 600 patients aged >50 y.o. ordinary treated in in-patient department of rehabilitation center. Risk factors for osteoporosis were assessed using IOF "One-minute osteoporosis risk test". 10-year probability of major osteoporotic fracture was calculated using Russian scale of FRAX on-line calculator.
Results
Assessment of osteoporosis risk factors revealed that 58.2% of responders had no risk factors, 6.8% had one risk factor, 3.8% - two, 0.6% - three, 9.1% - four, 21.5% - five or more risk factors. 45.8% of responders had experienced non-traumatic fractures in past, and a fractures occurred during rehabilitation procedures in 4.6% of ones. High probability of major osteoporotic fracture was revealed in 38% of all respondents, in particular in 45.7% of women and in 16.6% of men. The average 10-years risk for major osteoporotic fractures was 13.7% [1.6; 48.0] and for the hip fracture - 3.2% [0;16]. 8.6% of patients had 10-year absolute risk for major osteoporotic fractures more than 30%. 42.5% of respondents performed bone densitometry in the past. Osteoporosis was already diagnosed in 34.1% of respondents but only in 56.6% ($n=127$) of high fracture risk group. Among those who

never undergo densitometry there were 43.1% of patients with a high fracture risk. Anti-osteoporoitic treatment received just 31.0% among osteoporotic patients and 12.4% among subjects with high fracture risk.
Conclusions
45.7% of women and in 16.6% of men aged >50 y.o. ordinary treated in in-patient rehabilitation department have high risk of osteoporotic fracture, 41.2% patients had osteoporosis risk factors and 45.8% experienced non-traumatic fractures in past. Data indicate a high probability of non-traumatic fractures in those patients due to concomitant insufficient prescription of anti-osteoporotic medication.

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AEP240

Hypothyroidism effect on bone tissue

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Background
The issue of hypothyroidism effect on bone tissue is underinvestigated, due to the small number of studies. In addition, it's not easy to determine the effect of reduced thyroid function on bone strength due to the fact that these patients are usually elderly and have many additional factors for the development of osteoporosis. The purpose of the study is to assess the status of bone mineral density (BMD) in men with hypothyroidism.
Materials and methods
We have examined 35 men with primary hypothyroidism aged 28–69 years. Duration of disease (from the time of diagnosis and initiation of thyroid hormone replacement therapy) was 3 to 26 years. The average daily dose of levothyroxine was 125.5±16.5 μg. Patients were in a state of compensation (no complaints and a normal level of thyroid-stimulating hormone on the background of hormone therapy). The control group consisted of 25 healthy, clinically euthyroid men aged 25–49 years.
Results
Osteopenia of varying severity was detected in 11 (31.4 %), osteoporosis — in 8 (22.9 %) patients, and in the remaining 16 (45.7 %) persons, BMD was within normal limits. When comparing bone density graphs in patients of different age groups, it was found that with age, the frequency and severity of bone loss increases. Duration of disease has the most significant negative effect on the BMD in patients with hypothyroidism. Although the incidence of osteopenia in the group of patients with disease duration from 5 to 15 years is greater (55.0 %) than in persons with disease duration of more than 15 years (41.7 %), but osteoporosis is 2.5 times more likely in patients with longer duration of disease than in people with disease duration of 5–15 years.
Conclusions
Violations of bone mineral density, which are manifested in the development of osteopenia and osteoporosis, are observed in 54.3 % of men with primary hypothyroidism. Severity of changes in bone mineral density is directly proportional to the age, duration of thyroid hormone replacement therapy and inversely proportional to the body mass index.

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AEP241

Bone turnover markers and bone quality between patients with hyperthyroidism and primary hyperparathyroidism

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Background
Hyperthyroidism is widely known to be an important cause of secondary osteoporosis through the accelerated rate of bone turnover, while primary hyperparathyroidism is typically associated with loss of cortical bone and less so of trabecular bone, as seen on dual-energy x-ray absorptiometry (DXA). The evaluation of bone quality in these categories is not fully understood and needs further research. The aim of this study was to compare the bone quantity and quality, using bone turnover biomarkers, bone mineral density (BMD) and trabecular bone score (TBS) between patients with hyperthyroidism and primary hyperparathyroidism.
Methods
We performed a cross-sectional study on 52 patients evaluated in our clinic, between October 2018 and December 2019, 31 patients with hyperthyroidism (HT) and 21 patients with primary hyperparathyroidism (PHPT). The exclusion criteria were age <18 years, other secondary endocrine causes of osteoporosis. We analyzed demographic data, fragility fracture history, bone turnover markers, BMD and TBS.
Results
Among the 52 patients, the mean age was 58.1±11.8 years, female was the dominant gender (94.2%) and the mean body mass index was 28.2±5.8 kg/m^2. Patients from the PHPT group were significantly older (62.7 ±10.2 years vs 55±11.9 years, $P=0.01$), had a significantly higher serum calcium (10.9±0.5 mg/dl vs 9.6±0.3 mg/dl, $P<0.001$), parathormone level [103.5 (89.9–147.1) pg/ml vs 44.9 (32.8–46.9) pg/ml, $P<0.001$] and had more often prevalent fragility fractures (14.3% vs 6.5%, $P=0.35$). Additionally, a significantly higher percentage of patients with PHPT had a value of TBS <1.350 (85.7% vs 58.1%, $P=0.03$). Meanwhile, patients from the HT group had a significantly higher serum phosphorus (3.4±0.3 mg/dl vs 2.7±0.4 mg/dl, $P<0.001$) and bone turnover markers, like alkaline phosphatase (107.6± 41.2 U/l vs 78.1±23.4 U/l, $P=0.005$) and P1NP (122.3 (55.1–156) ng/ml vs 70.2 (50.4–82.5) ng/ml, $P=0.007$). We found that a TBS <1.350 had a sensitivity and specificity of 85.71% (95% CI, 63.66% to 96.95%) and 41.94% (95% CI, 24.55% to 60.92%), respectively, to predict bone fragility in patients with PHPT, with an accuracy of 59.62% (95% CI, 45.1% to 72.99%). However, there were no differences in BMD values on lumbar spine or hip between the two groups.
Conclusions
In conclusion, we found that patients with HT had higher bone turnover markers and patients with PHPT presented more often a TBS below 1.350. Thus, TBS could be a potential predictive marker for bone fragility in patients with PHPT.

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AEP242

Severe hypocalcemia and psuedotumor cerebri: Old, still not so well known relationship!

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Introduction
Clinical features of severe headache, vision loss, and papilledema; normal neuroimaging and elevated opening pressure on lumbar puncture are diagnostic of idiopathic intracranial hypertensions (IIH) or pseudotumor cerebri. Etiology is often attributed to obesity in young female patients. We present a rare case of Pseudotumor cerebri in a non-obese female patient with severe hypocalcemia.
Case
A 26 year old Hispanic female patient with past medical history of hypocalcemia, but off her medications, presented to ER for worsening headache for over a month. Without any specific triggers, she began having headaches in her bitemporal region. The pain was continuous, pressure-type, and 9/10 intensity at its worst. It was associated with nausea and blurring of vision and was refractory to ibuprofen. Patient endorsed severe muscle cramps on review of systems. Physical examination demonstrated mild distress due to the headache, positive Trousseau's sign, and bilateral papilledema. Laboratory studies revealed serum total calcium level of 4.8 mg/dl, albumin 3.5 g/dl, ionized calcium 0.71 mmol/l, serum phosphate 5.3 mg/dl, intact PTH 300.1 pg/ml, 25-OH Vitamin D 14.3 ng/ml and 1, 25-Dihydoxy Vitamin D 14.1 pg/ml, alkaline phosphatase 131 IU/l, 24-hour urinary calcium 48 mg/d and 24 hour urinary calcium/creatinine ratio 50 mg/g. Her MRI brain and MR venogram were unremarkable. Lumbar puncture had elevated opening pressure of 46 cm of H2O. The patient was started on Acetazolamide, oral calcium, and calcitriol without resolution of headaches and hypocalcemia. Acetazolamide was discontinued when she developed severe hypokalemia. With diagnosis of pseudohypoparathyroidism, the dose of elemental calcium was doubled and calcitriol dose increased to 1 mg BID with improvement of serum calcium, symptoms, and papilledema.
Discussion
While IIH could be associated with certain medications and systemic conditions, obesity or recent weight gain are the most commonly cited causes. Severe hypocalcemia is a rare and less known etiology of IIH. Cases of adult patients are reported with a variety of etiologies of severe hypocalcemia. Severe hypocalcemia leading to hypersecretion of cerebrospinal fluid is

postulated as a possible mechanism but evidence is lacking in literature. Chronic, rather than acute, severe hypocalcemia is likely to precipitate IIH. Visual symptoms, headache and papilledema are difficult to resolve with conventional medical therapy without correction of underlying severe hypocalcemia. We conclude that before considering surgical interventions for cases which are refractory to medical therapy, rare underlying conditions like severe hypocalcemia must be investigated and treated optimally.

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Diabetes, Obesity, Metabolism and Nutrition

AEP243

Heterogeneity and diagnostic features of diabetes mellitus types in young patients

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Heterogeneity of diabetes mellitus (DM) determines difficulties in the diabetes type verification and further treatment. With this regard, in 2019 WHO published a new classification of DM with categories: "hybrid types of diabetes" and "unclassified diabetes" intended for use in clinical practice.
Aim
To investigate the heterogeneity and clinical features of DM in young adult patients with an unspecified type of diabetes.
Materials and methods
50 young adult people±33.2 years (18–45 years) with an unspecified type of DM were included. All patients underwent a genetic testing for *GCK, HNF1α and HNF4α* genes mutations for MODY diagnosis. In all included patients we analyzed levels of GADA, IA-2A, ICA, IIA, ZnT8 antibodies and C-peptide levels during oral glucose tolerance test. Type 2 DM (T2DM) was established in patients no mutations and absence of β-cell antibodies.
Results
MODY2 was diagnosed in 46.94% of patients, MODY3 – 12.24%, MODY1 – 2.04%, T2DM – 28.57%, LADA – 2.04%, T1DM - 10.2%. MODY1 and LADA were established for only 2 patients and were not included in the statistical analysis. Debut of carbohydrate metabolism disorders in MODY2 and T1DM were diagnosed earlier than in other types of DM: 23 years [9; 41] and 25.4 years [18; 25] vs 30.5 years [10; 42] in MODY3 and 31.5 years [18; 45] in T2DM, (P <0.05). Median of HbA1c level did not differ between groups: in MODY2 6.4% [5.0; 10.3], MODY3 – 6.65% [5.6; 11.8], T2DM – 6.55% [5.2; 12.6], T1DM – 7.2% [6.4; 7.5], (P>0.05). BMI did not differ between groups: MODY2 – 20.6 kg/m² [15.6; 35.1], MODY3 -24.1 kg/m² [20.2; 29.3], T2DM – 23.1 kg/m² [18.5; 36.1], T1DM – 22.25 kg/m² [20.4; 23.0], (P>0.05). Significant differences were observed in C-peptide secretion levels: the lowest levels were observed in patients with T2DM (0 min – 1.29 ng/ml [0.64; 3.91], 60 min – 6.7 ng/ml [5.6; 12.2], 120 min – 4.45 ng/ml [3.1; 10.21]) compared with patients with other groups (MODY2, MODY3), (P <0.05).
Conclusion
The study demonstrates the significant clinical heterogeneity of DM in the young age group. Genetic and immunological tests are necessary to verify monogenic and autoimmune forms of DM and also important for determining further management. Young patients with T2DM require further studies, in order to identify underlying mechanisms of impaired insulin secretion.

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AEP244

Hemoglobin glycation index is associated with incident chronic kidney disease in subjects with impaired glucose metabolism: A 10-year longitudinal cohort study

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Objectives
We investigated associations between hemoglobin glycation index (HGI) and incident chronic kidney disease (CKD) in treatment naïve subjects with prediabetes or diabetes.
Methods
A prospective cohort study was conducted in 2,187 subjects with prediabetes or diabetes. The HGI was calculated as the measured HbA1c minuspredicted HbA1c, which was calculated from the linear relationship between HbA1c and fastingplasma glucose levels. Incident CKD was defined as occurring if eGFR decreased toless than 60 ml/min per 1.73 m^2 and decreased by more than 25% from baseline during follow up. The hazard ratio (HR) for incident CKD was calculated using Cox models.
Results
The overall prevalence of CKD was 335 (15.3%) during the 10-year follow-up period. The prevalence of CKD significantly increased from the first to third tertile of HGI. In multivariate analysis, the highest HGI tertile group showed the highest adjusted HR for incident CKD (HR, 1.57; 95% CI, 1.06–2.34) and this was significant even after adjustment for HbA1c.
Conclusion
High HGI was associated with increased risk for incident CKD in treatment naïve subjects with prediabetes or diabetes. These finding suggest that HGI might provide for predicting CKD in these patients regardless of HbA1c levels.

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AEP245

Assessment of arrhythmia risk due to hypoglycemia with continuous glucose monitoring device and 24-hour holter monitoring

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Previous studies have shown increased hypoglycemia-associated cardiac arrhythmia and mortality in patients with type 2 diabetes and cardiovascular disease.
In this study, we aimed to evaluate the response of gastrointestinal hormones and glucoregulatory hormones to the oral glucose tolerance test in patients who were diagnosed with reactive hypoglycemia and to evaluate the risk of arrhythmia with long-holter ECG measurements in patients with a diagnosis of reactive hypoglycemia. In this prospective observation study, 64 patients (F / M: 42/22) who admitted to our clinic with reactive hypoglycemia-like complaints were subjected to oral glucose tolerance test with mixed meal. Patients with hypoglycemia symptoms who had plasma glucose values below 55 mg/dl in the first 4 hours of postprandial period were considered as reactive hypoglycemia.
Continuous glucose monitoring and 72-hour holter ECG examinations were performed synchronously in these patients. At the same time, prolonged OGTT test was performed in these patients. Glucose, insulin, leptin, glucagon, GLP-1, cortisol levels were evaluated in 0,15,30,60,90,120,180,240,300 minutes. Postprandial median glucose values were at hypoglycemic levels at 180 and 240 minutes.
During the test protocol a decrease of 26 mg/dl glucose in the hypoglycemic period, an increase of 21.4 pg/ml in GLP-1 levels, a decrease of 20.4 U/ml in insulin levels, an increase in glucagon level of 18.9 pg/ml, and an increase in cortisol level of 2.9 µg/dl were detected. Continuous glucose monitoring revealed symptomatic hypoglycemia in 2 of 7 patients (glucose <55 mg/dl). At least one hypoglycemic value was detected in 6 of 7 patients. No biochemical or clinical hypoglycemia was detected in one patient. 11 ectopic ventricular beats were detected in 2 patients with severe hypoglycemia.
Although the symptoms of postprandial hypoglycemia are seen in many individuals in the community, the frequency of reactive hypoglycemia was lower than expected when standard diagnostic tests were applied to these patients. Atrial and ventricular ectopic pulses may be seen in patients with reactive hypoglycemia, although severe cardiac arrhythmia is not observed. The mechanisms involved in the etiology of reactive hypoglycemia have still not been elucidated. We can speculate that the increase in GLP-1 and leptin hormone levels may be responsible for postprandial hypoglycemia.

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AEP246

Insights from whole exome sequencing in a Maltese cohort with gestational diabetes

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Background
Gestational diabetes (GDM) can be driven by mutations or rare variants in various genes associated with monogenic or atypical forms of diabetes. The reported frequency of monogenic defects of beta cell function in GDM varies extensively, in part due to differences in ethnicity, patient ascertainment criteria and techniques used for genetic analysis. The objective was to evaluate the frequency and molecular spectrum of mutations in a curated list of genes associated with monogenic/atypical diabetes in non-obese women of Maltese ethnicity with GDM.
Method
30 non-obese Maltese women who met the International Association of the Diabetes and Pregnancy Study Group (IADPSG) criteria for diagnosis of GDM and with a first-degree relative with non-autoimmune diabetes were included in this study. Whole exome capture and high throughput sequencing was carried out. Rare sequence variants were filtered, annotated and prioritized according to the American College for Medical Genetics guidelines. For selected missense variants we explored effects on protein stability and structure through homology predictions or PDB structures using in-silico tools.
Results
In total, we identified three pathogenic mutations and twelve variants of uncertain significance (VUS). The disease-causing mutations comprise a nonsense mutation in *GCK*, an insertion-frameshift at a mutational hotspot in *HNF1A* and a missense substitution in *ABCC8*. Critically, the *ABCC8* mutation leads to significant changes in interatomic interactions and to expansion of protein cavity volume, with resulting destabilising effects. Damaging VUS in *PDX1, KLF11, DYRK1B, TRMT10A, AKT2, BLK, GLIS3* and *NKX6-1* were detected, having either conflicting pathogenicity interpretationsor insufficient evidence for pathogenicity from in-vitro studies. Novel *NEUROG3* and *CEL* VUS were also detected. Stereochemical analysis reveals that the missense variants described in *NEUROG3, DYRK1B, TRMT10A*and*AKT2* have destabilising effects. Genotype-phenotype correlations for all detected variants are described, including associations with anthropometric traits, OGTT, HOMA-IR, treatment and post-pregnancy follow-up data where available. We show that GDM cases who were carriers of either pathogenic mutations or damaging VUS had a younger age of GDM diagnosis than females where no variant of interest was identified. (29 vs 32 years, $P=0.039$).
Conclusion
This study provides the first insightinto an underlying monogenic aetiology in non-obese women with GDM from a high-prevalence island population. It suggests that monogenic variants constitute an underestimated cause of diabetes detected in pregnancy, and that careful evaluation of GDM probands to identify monogenic disease subtypes is indicated.

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AEP247

Features of sarcopenia and body composition measured with bioimpedance in patients with diabetes mellitus type 2

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Aim
To investigate the association between presence of sarcopenia and type 2 diabetes mellitus (T2DM).
Methods
The study included 76 women over 60 years old (Me72[67;77] years). Patients were examined with evaluation of muscle mass, muscle strength and muscle function. Skeletal muscle mass index (SMMI) was evaluated with bioimpedance testing. Sarcopenia was defined as a SMMI ≤6,75 kg/m^2. Peripheral neuropathy was studied with calculation of NIS-LL scale (max points=96). Patients were divided into 2 groups: with sarcopenia (S+, $n=29$) and without sarcopenia (S–, $n=47$). We did not find any significant difference between age and diabetes duration in S+ and S- groups. Multivariable logistic regression model were adjusted for age. We plotted a ROC curve to compare the diagnostic accuracy of the anthropometric indicators and to find the optimal cut-off values of each indicators.
Results
The frequency of HbA1c level more then 8% were 72% in S+group and 49% in group S– ($P=0.041$). S+ group less frequently received metformin ($P=0.011$) and insulin ($P=0.044$). Patients with sarcopenia demonstrated more often chronic kidney disease (70%) than S– (27%, $P=0.024$). Diabetic neuropathy was more severein S+group than in S-group (NIS-LL: 12[7;17] vs 6 [4,8], $P<0.001$). Frequency of falls and fractures was noted more often in S+ group in comparison with S-group (66% vs 36%, $P=0.013$, 36% vs 13%, $P=0.003$). Patients S+had smaller BMI vs S- (25.2 [20,72;29,24] vs 31.6[28,9;35,9] kg/m^2, $P<0.001$), waist (89,5[83,75;100,5] vs 104[100;112] cm, $P<0.001$) and neck circumferences (37[22,5;38] vs 40[35;40] cm, $P<0.001$). According bioimpedance measurement S+patients was differed with more pronounced decrease of skeletal muscle massvs S-patients (16.5[14,8;17,3] vs 19,2[18,3;21,6] kg, $P<0.001$), fat mass (22.35[18,65;29,175] vs 31.8[27,4;40] kg, $P=0.006$) and mineralmass of bones (1.83[1,73;2,04] vs 2,18[2,09;2,45] kg, $P<0.001$). The multivariable logistic regression analysis revealed the associations of presence of sarcopenia in T2DM patients with NISLL more then 11 points (OR-22,14;95% CI[3,68-133,30], $P=0.001$). BMI cut-off points to identify sarcopeniasubjects was ≤29 kg/m^2 (sensitivity-87.2%; specificity-72.4%) for women with T2DM. Waist circumference cut-off pointsto identify sarcopenia subjects was ≤102,5 cm (sensitivity-85.1%; specificity-65.5%) for women with T2DM. Shoulder andlower leg circumferences were ≤30,5 cm (sensitivity-85.1%; specificity-65.5%) and ≤36 cm (sensitivity-91.5%; specificity 69%) for women with T2DM.
Conclusion
Sarcopenia was more often detected in patients with more severe peripheral neuropathy, poor glycemic control and history of falls. S+ patients characterized with more severe changes in the body composition not only in the skeletal muss, but also in the amount of fat mass and bone mineral density.

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AEP248

Evaluation of the endocrine cells ratio in the pancreas of rats with type 2 diabetes mellitus following long-term therapy with incretin mimetics and their combination with sulfonylureas drugs

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Introduction
New medicinal products that have been introduced into first-line therapy for type 2 diabetes mellitus (T2DM) include glucagon-like peptide-1 receptor agonists (GLP-1ra) and dipeptidyl peptidase-4 inhibitors (DPP-4i). These products have been shown to increase beta-cell proliferation. Some studies also demonstrated an increase in pancreatic alpha-cell proliferation. Various sulfonylureas drugs (SU) have been shown to produce different effects on apoptosis pancreatic cells. Therefore, we are interested in evaluating the effects of treatment with combinations of incretin mimetics with SU on pancreatic cells.
Goal of the study
The goal of this study was to evaluate the effects of long-term therapy with combinations of incretin mimetics and SU on the ratio of alpha- and beta-cells in a model of type 2 diabetes in 12-month-old rats.
Materials and methods
Streptozotocin-nicotinamide-induced model of type 2 diabetes was used. The animals received treatment according to the assigned groups over a period of 24 months. Treatment groups (5 animals per group): 1) control group (healthy animals); 2) animals with T2DM without any treatment; 3) animals with T2DM treated with Exenatide; 4) Vildagliptin; 5) Exanatide+ Gliclazide; 6) Vildagliptin+ Gliclazide; 7) Exenatide + Glibenclamide; 8) Vildagliptin + Glibenclamide. After the end of treatment, immunohistochemistry using anti-glucagon and anti-insulin antibodies was carried out.
Results
A volume ratio of alpha- and beta-cells of the pancreas was determined relative to the area of the pancreatic islets. The volumes of beta cells in the healthy control group was comparable to those in the groups receiving monotherapy with Exenatide,Vildagliptin, their combination with SU. There were statistically significant differences in the volumes of alpha-cells in the groups receiving Glibenclamide monotherapy andin combination with GLP1ra or DPP4iin comparison with the healthy control.

Conclusions
24-week treatment with GLP1ra and DPP4i resulted in normalization of both beta and alpha cell contents. The normalization of the content of alpha-cells in animals treated with Gliclazide-containing combinations was comparable to that observed in the groups receiving monotherapy with GLP1ra, DPP4i, and the healthy control group while the number of alpha-cells in the groups receiving incretin mimetics in combination with Glibenclamide was similar to the content of these cells observed in the group with untreated T2DM.

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AEP249

A multi-center, randomized, double-blind, parallel, active-controlled phase III clinical trial to evaluate the efficacy and safety of controlled-release pregabalin and immediate-release pregabalin in diabetic peripheral neuropathic pain

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Pregabalin is a highly used drug for the effective treatment of diabetic neuropathic pain. This study compared the efficacy and safety of a controlled-release (CR) Pregabalin tablet (GLA5PR GLARS-NF1) with an immediate-release (IR) Pregabalin capsuleafter 12 week administration in patients with diabetic peripheral neuropathy. In multicenter, randomized, double- blind, active- controlled, parallel- group, phase III study, the primary outcome was to confirm that CR pregabalin with once daily (after meal in the evening) is clinically non-inferior to IR pregabalin with twice daily regimen in improving the meanDaily Pain Rating Scale (DPRS) for the treatment of peripheral neuropathic pain. The efficacy endpoints in patients with diabetic peripheral neuropathic pain which were the target diseases, and patients who received and did not receive restricted concomitant medications during the clinical study were analyzed. 59 subjects in the study group and 58 subjects in the control group was allogated. Themean DPRS adjusted by using the baseline mean DPRS as a covariate was 3.26±0.23 in the study group and 3.41±0.32 in the control group (LS mean difference, –0.16; 95% CI, –0.79 to 0.48), indicating that the study group was not-inferior to the control group. In addition, no consistent trend was seen in comparison of sleep indicator between the groups for each subgroup, but at Week 12 after administration of the investigational product, a tendency of decrease was observed, similar to the result of the primary analysis. The overall adverse event profile of the study groupand control group was similar, and no serious ADR was observed. CR pregabalin treatment for 12 weeks was non-inferior compared to IR pregabalin in improvement of pain in patients with diabetic peripheralneuropathy. CR pregabalin can be used effectively and safely in diabetic peripheral neuropathic pain, and it is expected thattreatment effects can be maximized by improving patients' treatment compliance since the drug isadministered once daily.

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AEP250

Gestational diabetes in korea: Temporal trends in prevalence, treatment, and short-term consequences from a national health insurance claims database 2012 – 2016

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Aims
This population-based cross-sectional study aimed to investigate the recent trends in the prevalence and treatment of gestational diabetes mellitus (GDM) in a nationally representative sample of Korean patients. We also investigated trends of annual prevalence rate of pregnancy-induced hypertension (PIH) and cesarean section (C-section) in patients with GDM.
Methods
We used data from the Health Insurance Review and Assessment-National Patient Sample (HIRA-NPS) database, 2012–2016. GDM, PIH, and C-section weredefined according to ICD-10 codes. Non-GDM (n=54, 346) and GDM (n=8,137) patients between 2012 and 2016 were analyzed for each year.
Results
The annual increase of the prevalence of GDM was 11.2% in 2012–2016, with a significant continuous increasing trend (P<0.0001). Age group-stratified analysis showed that theannual prevalence of GDM significantly increased in below 40 years group, but statistically insignificant increasing trends in above 40 years group. Regarding treatment pattern during pregnancy in patients with GDM, there was no statistically significant increasing or decreasing trend. Diet only treatment showed increasing trend and insulin treatment showed decreasing trend, but both were statistically insignificant. PIH prevalence rate was shown significantly increasing trend by year, but statistically insignificant in both unadjusted and adjusted. Annual increase of C-section rate above 5% in GDM was statistically significant in both unadjusted and adjusted for age and PIH.
Conclusion
The prevalence of GDM in Korean women and C-section rates in women with GDM showed significantly increasing trendfrom 2012 to 2016. The present study is the first study to investigate the prevalence and treatment of gestational diabetes mellitus (GDM) and rates of pregnancy-induced hypertension (PIH) and cesarean section between women with and those without GDM in Korea using a large national database. There is a need for further efforts to monitor this trend and to identify associated risk factors for GDM.

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AEP251

Twin pregnancy with gestational diabetes mellitus: Maternal and fetal outcomes

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Introduction
In singleton pregnancies, gestational diabetes mellitus (GDM) results in an increased risk for maternal and neonatal complications. In twin pregnancies, however, the effect of GDM on maternal and neonatal complications appears to be different in comparison to singletons. The few studies that investigated the consequences of GDM in twin pregnancies are small and present conflicting evidence, with some finding no difference in perinatal outcomes between GDM and non-GDM twins and others even demonstrating better outcomes.
Objetive
To Compare maternal and fetal outcomes in pregnant women with and without GDM in a twin pregnancy.
Methods
Observational and retrospective study comparing maternal and fetal outcomes in 42 women having a twin pregnancy complicated with GDM followed in a Portuguese tertiary hospital whose deliveries occurred between 2011 and 2018, with 83 pregnant women with twin pregnancies without GDM whose delivery occurred in 2018.
Results
There was no difference in maternal mean age (32.7±4.8 vs 32.8±4.8 years-old, P=0.936) and in fertility treatment rate (45.2% vs 34.9%, P=0.114), in both groups. The pre-pregnancy IMC and percentage of excessive weight gain was higher in the GDM group, with 24.9 (IQR: 22.4–28.5) vs 23.8 (IQR: 21.2–25.5) kg/m², P=0.007 and 10.7% vs 0%, P=0.005, respectively. No difference between the groups was found for: abortion rates, hydramnios, fetal death, chorionicity, induced and chronic hypertension. The GDM group it seems to had a higher risk of having preeclampsia, but without statistical significance (14.3% vs 7.2%, P=0.074). Regarding fetal outcomes, no difference was found between the two groups for hypoglycemia, hyperbilirubinemia, respiratory distress syndrome (RDS), NICU admission, birth trauma or neonatal death rates. Both groups presented a high prematurity rate (73.8% vs 72.3%, P=0.799, with and without GDM, respectively). There was a higher prevalence ofsmall for gestational age (SGA) babies in the group without GDM (40% vs 27.4%, P=0.049). None of groups had newborns with macrosomia or large for gestacional age (LGA).
Conclusion
There was no difference between maternal outcomes in twin pregnancy with or without GDM. Nevertheless, and although the results were not sig-

nificant, the group with GDM had a higher prevalence of preeclampsia, as described in other studies. Twin pregnancy complicated with GDM is not associated with neonatal morbidity occurrence, characteristic of the newborn from a diabetic mother observed in singleton pregnancy and this diagnosis seems to be protective for SGA occurrence.

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AEP252

Immunomodulatory and anti-diabetic actions of a structurally-modified analogue of esculentin-2CHa isolated from the skin secretion of the frog, lithobates chiricahuensis (ranidae)

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Aim
Our previousstudies have shown evidence for insulin-releasing actions of some amphibian skin peptides; including esculentin-2CHa. However, there is a need to further improve the potency of some of this peptides and to characterize their other beneficial effects. This study investigates the effect of a Leu[31]→Lys substitution on the insulin-releasing and immunomodulatory effects of esculentin-2CHa.
Methods
BRIN-BD11 cells were incubated for 20 min in a buffer containing esculentin-2CHa or [L31K] esculentin-2CHa at 5.6 mM or 16.7 mM glucose. Effects of [L31K]esculentin-2CHa in the presence of established modulatorsof insulin secretion were also examined. Acute *in vivo* effects of [L31K] esculentin-2CHa on glucose tolerance and insulin secretion were investigated in high fat fed mice. Expression of MHC I, II and cytokine release from [L31K] esculentin-2CHa –treated bone marrow dendritic cells (BM-DCs) were investigated by Flow Cytometry and ELISA.
Results
Leu[31]→Lys substitution significantly enhanced the insulinotropic effects of [L31K] esculentin-2CHa (0.01 nM–1 μM; 1.1–1.7-fold; $P<0.05$–0.001) compared with the native peptide. At 16.7 mM glucose, insulin-release in [L31K] esculentin-2CHa-treated cells increased by 1.3-fold ($P<0.001$). These actions were not associated with significant LDH release. Diazoxide (200 μM, 40%, $P<0.01$), verapamil (50 μM, 58%, $P<0.001$) and removal of extracellular calcium (56%, $P<0.001$) significantly inhibited insulin-releasing effects of [L31K] esculentin-2CHa. Increased insulin-release was observed in incubations involving [L31K]esculentin-2CHa and KCl (30 mM, 1.9-fold, $P<.001$), IBMX (200 μM, 3.1-fold, $P<0.001$) or tolbutamide (200 μM, 3.8-fold, $P<0.001$). [L31K] esculentin-2CHa improved glucose tolerance by 42% ($P<0.05$) and insulin secretion by 57% ($P<0.01$) in high-fat fed mice. The expression of MHC I and II, or the release of IL-10, IL-12 and IL-23 from BM-DCs were unaffected.
Conclusions
This study indicated that the Leu[31]→Lys-substitution improved the anti-diabetic actions of esculentin-2CHa without generating pro-inflammatory immune responses.

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AEP253

Congenital hyperinsulinemic hypoglycemia: A case report

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Introduction
Persistent endogenous hyperinsulinemic hypoglycemia in neonates (congenital hyperinsulinism; CHI) is usually due to monogenetic gene variants affecting the insulin secretion. The genetic cause is known in about 50% of patients. We present a new variant within the *short-chain L-3-hydroxyacyl-CoA dehydrogenase (HADH)* gene causing CHI in two cousins.
Methods
The cases of two patients with CHI are presented with a follow-up of >30 years.
Results/Case Reports
A 32-year-old man (patient 1) and his 30-year-old cousin (patient 2) with CHI were referred to the outpatient clinic for treatment. According to the pediatric notes, the first hospitalization was at day 17 after birth in patient 1 (apnea with cyanosis during breastfeeding) and at day 10 in patient 2 (muscular hypotonia and sucking weakness). The diagnosis of CHI was established in both patients during the first hospitalization. A therapy with Diazoxide was initiated. The growth charts of both patients documented a disproportionate increase in weight in relation to height in childhood and adolescence, mainly due to recurrent hypoglycemic events with snacking of carbohydrates. In adulthood, the frequencies of hypoglycemic episodes increased leading to the referral. The patients belong to consanguineous family.
Investigation
1) A genetic analysis was performed in the *ABCC8*, *KCNJ11* and *HADH* genes resulting in a novel homozygous pathogenic variant in the *HADH* gene (*HADH*-variant c.796G>T). The disease is autosomal recessive. 2) Based on the finding an acylcarnitine-profile was performed showing an increased plasma 3-OHButyryl-carnitine, consistent with a dysfunction of the HADH enzyme. 3) Histologically, CHI is associated with pancreatic nesidioblastosis, which can be focal, atypical or diffuse. We have previously shown that nesidioblastosis can be morphologically characterized by targeting GLP-1 receptors, which are overexpressed. Therefore, a GLP-1-receptor-PET/CT with ^{68}Gallium-DOTA-exendinwas performed showing significantly increased uptake in the whole pancreas in both patients compatible with a diffuse form of nesidioblastosis. A surgical procedure was, therefore, not a therapeutic option.
Therapy
Intermittent monitoring with continuous glucose monitoring system and a somatostatin analogue was administered in addition to Diazoxide resulting in a significant decrease in hypoglycemic events. Patient 1 lost 24 kg within 9 months due to a decrease in snacking.
Conclusion
- A genetic work-up is mandatory in patients with CHI.
- The increased uptake of the GLP-1-receptor-PET/CT indicates an overexpression of GLP-1 receptor in this condition. The pathophysiological role of this finding is unclear.
- Therapy with Diazoxide and Octreotide has to be evaluated in adults with CHI and recurrent hypoglycaemias.

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AEP254

Chronic activation of adaptive immunity in type 2 diabetes

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Context
Type 2 diabetes (T2D) is associated with an increased incidence of infections and several cancers. Although low-grade inflammation and certain immune defects have been found in diabetic patients, the role of adaptive immune response remains to be fully elucidated.
Objective
We aimed to explore whether patients with T2D show defects in the activation of T cells.
Design
Immune cell phenotypes, T cell functional reactivity, surface receptors involved in T cell activation, and serum cytokines were compared between 24 T2D patients and 24-age, gender and BMI-matched healthy controls.

Results
Higher frequencies of CD4 T lymphocytes were observed in T2D patients than in healthy controls. Moreover, CD4 T showed augmented expression of co-stimulatory receptor CD28. After PMA/ionomycin stimulation, the percentages of IFNγ, IL-10 and p35-producing CD4 and CD8 T cells were significantly increased in T2D patients. CD4 and CD8 T cells showed augmented production of IFNγ, IL-10, IL-13, IL-17 and p35 cytokines. The percentages of regulatory T cells, B cells, monocytes and dendritic cells were comparable between T2D patients and healthy controls, however, B cells and CD16-positive monocytes expressed more surface MHC class I molecules. The serum levels of IL-10 were increased, while MIG were reduced in T2D patients. The frequencies of certain subtypes of T cells and production of cytokines by T cells were positively correlated to fasting blood glucose, HbA1c and IL-10, while negatively correlated to MIG.
Conclusions
These data indicate that hyperglycemia and chronic inflammation in T2D may lead to sustained activation of T cells, which may result in T cell dysfunction and unresponsiveness.

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Thrombocyting haemostasis in children with diabetes mellitus type I

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Thrombocytes play important role in pathogenesis of diabetic vascular complications.
Aim
To study peculiarities of thrombocyting haemostasisin children with diabetes mellitus type 1 (T1DM).
Patients and methods
120 children (66 boys, 54 girls) 3–17 y.o. with T1DM were examined. The duration of the disease was: less than 1 year in 29 patients (HbAc1 7.5±0.4%) – group 1, from 1 to 5 years in 41 patients (HbAc1 8.7±1.4%) – group 2, more then 5 years in 50 children (HbAc1 11.4±2.2%) – group 3. Control group: 60 healthy children 3–17 y.o. The indexes of trombocyte aggregation (degree, speed and time of aggregation) measured by laser method with different inductors (ADP, adrenalin, kollagen) and intravascular aggregation were evaluated.
Results
Level of adrenalin-stimulating aggregation, speed of kollagen-stimulating aggregation and intravascular aggregation of thrombocytes were increased in group 1 in comparance of control group ($P<0,05$). Levels of ADP- and kollagen-stimulating aggregation ($P<0,05$) and intravascular aggregation ($P<0,001$) were also increased in group 2. Decrease of aggregation time was revealed in this group ($P<0,05$). Increase of all indexes of functional activity of thrombocytes ($P<0,05$) and increase of intravascular aggregation ($P<0,001$) were found in patients of group 3 in comparance of control group.
Conclusions
The changes of thrombocyting haemostasisin children with T1DM were reveald. Functional activity of thrombocytes in this children appeared to increase in correlation with duration of the disease and it may demand treatment.

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Fatty liver, irrespective of ethnicity, is associated with reduced insulin clearance and insulin resistance in obese youths

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Background
Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common chronic liver disease in Western countries and identifies people at high risk to develop metabolic and cardiovascular disease. Fatty liver has been associated with reduced endogenous insulin clearance (EIC) and hepatic insulin resistance (HIRI), which are early features of type 2 diabetes. These relationships however might be differentially affected by the ethnic background, as populations of African ancestry typically have reduced intrahepatic fat content (HFF%) associated with impaired insulin clearance and sensitivity. Therefore, the aim of this study was to evaluatethe impact of the ethnicity on the relationships between HFF%, EIC and HIRI.
Methods
We analyzed cross-sectional and longitudinal data from the Yale Pediatric NAFLD cohort, a large ($n=620$) and well characterized cohort of overweight and obese adolescents from the three most prevalent racial and ethnic groups in the United States. The HFF% was quantified by a validated magnetic resonance imaging (MRI) method at baseline and after a median follow up of 2 years. Insulin secretion rate (ISR), EIC and HIRI were assessed during 3-hour, 9-point oral glucose tolerance tests (OGTTs) by modeling glucose, insulin, and C-peptide data.
Results
African Americans ($n=172$) exhibited the lowest HFF% and a prevalence of NAFLD less than half of Caucasians ($n=229$) and one third of Hispanics ($n=231$). Furthermore, African Americans had lower EIC and glucose-stimulated ISR, but similar HIRI and plasma insulin levels, compared with other ethnic groups. The HFF% correlated with EIC (std. $\beta=-0.13$, $P=0.0003$) and HIRI (std. $\beta=0.17$, $P<0.0001$), irrespective of the ethnic background, after adjustment for age, sex, ethnicity, BMI z-score, pubertal status, and plasma glucose levels. African Americans showed a lower susceptibility to intrahepatic fat accumulation at follow up, with a two-fold higher (52%) prevalence of adolescents whose HFF% remained stable (change $<\pm$ 1%) compared with Caucasians (28%) and Hispanics (20%) ($P=0.036$). Nevertheless, changes in HFF% over timewere associated with changes in EIC ($r=-0.25$, $P=0.02$) and HIRI ($r=0.22$, $P=0.04$) across all groups, without ethnic differences.
Conclusions
This study demonstrates that intrahepatic fat accumulation is associated with reduced EIC and HIRI in obese youths, irrespective of their ethnic background. Our data dissect the metabolic characteristics of populations of African ancestry and provide novel evidence about the pathogenetic role of liver steatosis in the development of hepatic metabolic abnormalities associated with type 2 diabetes progression.

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Abstract withdrawn

AEP258

Are we being too demanding with obese pregnant women with gestational diabetes?

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Introduction
Nutritional therapy is essential in the treatment of gestational diabetes mellitus (GDM). International recommendations suggest a target of 5–9 kg weight gain in obese women during pregnancy. However, some studies advocate a reduced weight gain (<5 kg) due to better obstetric and neonatal outcomes, compared to an adequate or excessive weight gain.
Aim
To compare obstetric and neonatal outcomes of obese women with GDM with insufficient, adequate and excessive weight gain during pregnancy.
Methods
A cohort of 4563 women with GDM, single fetus pregnancy and pre-pregnancy BMI ≥ 30 kg/m^2 from the Portuguese Registry of GDM was analysed.

T-test and Mann-Whitney U test were used to compare two groups for parametric and non-parametric variables, respectively. Chi square test was used to study differences between categorical variables. A level of significance $\alpha=0.05$ was noted.
Results
Women presented a mean age of 33.29±5.26 years old and a median pre-pregnancy BMI of 34.86 (IQR 5.36) kg/m^2. GDM were diagnosed in median at 23 (IQR 16) weeks of pregnancy. From all, 34.5%, 30.4% and 35.2% had insufficient, adequate and excessive gestational weight gain. The newborn's growth was evaluated according to Fenton curves in 98% of cases. Women with insufficient gain weight had a higher prevalence of small for gestational age (SGA), compared with the other two groups (13.1% vs 8.3% vs 7.5%, $P<0.0001$). By multiple logistic regression, insufficient weight gain during pregnancy was found to increase the possibility of SGA by 76% (OR=1.755, 95% CI=1.436–2.145, $P<0.0001$). A lower value of HbA1c in 3rd trimester was presented in pregnancies with insufficient weight gain (5.29±0.60 vs 5.34±0.45 vs 5.45±0.52, OR=0.612, 95% CI=0.518–0.724, $P<0.001$). Post-partum reclassification of diabetes was performed in 3123 women. Those with insufficient gestational weight gain had a higher prevalence of normal results), compared with the other two groups (91.4% vs 88.7% vs 88.5%, $P=0.004$ and $P=0.002$). No significant differences were found regarding week of diagnosis, treatment with insulin, gestational age, prematurity, global neonatal morbidity, neonatal hypoglycaemia or neonatal intensive care hospitalization between women with insufficient gain weight and the other two groups.
Conclusion
In clinical practice, we are very strict regarding weight gain in obese pregnant women, even those with insufficient weight gain. However, our data seems to validate the international recommendations because reduced weight gain could be harmful to the newborn growth.

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Randomized controlled trial of different intensities of glycemic control in women with gestational diabetes

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Background and aims
Current glycaemic treatment targets for women with gestational diabetes (GDM) are controversial. The aim of the study was to compare the effect of different intensities of glycaemic control in pregnant women with GDM on perinatal outcomes.
Materials and methods
Pregnant women in the 8th to 31st week of gestation were randomly assigned to 2 groups per target glycaemic levels: GDM1 (very tight glycaemic targets, fasting blood glucose (FBG) <5.1 mmol/l and <7.0 mmol/l postprandial) and GDM2 (less tight glycaemic targets, <5.3 mmol/l and <7.8 mmol/l, respectively). GDM was diagnosed according to World Health Organization (WHO 2013) criteria. Women were instructed on lifestyle changes and blood glucose monitoring. Insulin therapy was started if target blood glucose levels were exceeded in 2 or more measurements per week in GDM1 and in more than 1/3 of measurements per week in GDM2 group. The primary outcome was the incidence of large for gestational age (LGA) infants.
Results
A total of 616 women were randomly assigned to the study groups: GDM1 ($N=310$) and GDM2 ($N=306$). The rates of LGA infants were similar between the groups (13.7% and 15.6%, for GDM1 and GDM2, respectively, $P=0.550$). There were no significant differences in secondary outcomes including composite of stillbirth or perinatal death and severe neonatal morbidity (nerve palsy, bone fracture and shoulder dystocia) (2.5% and 2.1%, $P=1.0$), gestational age at birth (39.0±1.3 vs 38.9±1.5 weeks, $P=0.224$), birthweight (3423±492 vs 3429±539 g, $P=0.884$), macrosomia (birth weight >4000 g) (12.6% vs 13.3%, $P=0.900$), small-for-gestational age infant (9.8% vs 8.5%, $P=0.660$), neonatal hypoglycaemia (5.9% vs 6.3%, $P=1.0$), admission to the neonatal nursery (4.0% vs 5.3%, $P=0.598$), pre-eclampsia (15.0% vs 15.8%, $P=0.813$), cesarean delivery rate (24.3% vs 29.4%, $P=0.260$), gestational weight gain (9.8±6.7 vs 10.9±6.3 kg, $P=0.081$), any perineal trauma (27.2 vs 27.0%, $P=0.9$) and induction of labor (34.2% vs 30%, $P=0,313$) for GDM1 and GDM2, respectively. GDM1 group achieved lower mean FBG (4.8±0.4 mmol/l vs 4.9±0.5 mmol/l, $P=0.047$) and mean postprandial glucose values (6.1±0.5 mmol/l vs 6.3±0.6 mmol/l, $P<0.001$). The proportion of women prescribed with insulin was higher in GDM1 compared to GDM2 group (45.5% and 26.5%, $P<0.001$).
Conclusion
There were no clear differences in perinatal outcomes between the groups of women receiving very tight and less tight glycaemic targets. The frequency of insulin prescription was substantially higher in the very tight glycemic control arm.

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Weight loss through lifestyle modification or liraglutide is associated with improvement of NAFLD severity and changes in amino acid concentrations

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Introduction
Non-alcoholic fatty liver disease (NAFLD), defined as excess fat accumulation in the liver, is increasingly prevalent due to obesity. NAFLD may lead to steatohepatitis and eventually cirrhosis. Weight loss, either through diet and exercise or medications such as the glucagon-like peptide-1 agonist liraglutide, improves transaminitis, a marker of NAFLD severity. Visceral obesity is associated with increased plasma levels of the amino acids alanine, phenylalanine, tryptophan and tyrosine[1]. The glutamate-serine-glycine (GSG) index (= glutamate/[serine+glycine]), derived from the amino acids glutamate, serine and glycine which are involved in glutathione synthesis, is positively associated with hepatic insulin resistance and with hepatic inflammation on liver biopsy[2]. In this study we compared effects of weight loss from either lifestyle modification or liraglutide therapy on serum transaminases and amino acid profiles.
Methods
Thirty obese (mean age 40.7±9.1 years, BMI 33.2±3.6 kg/m^2, weight 96.4±15.8 kg) adults with NAFLD and transaminitis (mean ALT 87±34 U/L, AST 48±21 U/L) were randomized to either dieting (decrease by 400 kilocalories/day) plus moderate-intensity exercise (200 minutes/week) to induce ≥5% weight loss (DE group, $n=15$), or to liraglutide 3 mg daily therapy (LI group, $n=15$) with standard weight loss advice for 12 weeks. We measured serum alanine (ALT) and aspartate (AST) aminotransferases, amino acid profile, and insulin resistance calculated using homeostasis model assessment (HOMA).
Results
At baseline, plasma ALT and AST were positively associated with the GSG index, alanine and tyrosine levels. Both DE and LI groups had significant ($P<0.01$) and similar ($P>0.05$ between groups) reductions in weight (–3.3±2.9 vs –3.1±1.8 kg respectively), HOMA (–2.96±2.25 vs 2.03±2.11), ALT (–42±34 vs –34±27 U/l) and AST (–23±24 vs –10±15 U/l). GSG decreased in both groups, while alanine, phenylalanine, tyrosine and tryptophan decreased only with liraglutide.
Conclusion
Weight loss by either caloric restriction or liraglutide therapy is linked to reduction in severity of NAFLD, as indicated by decreases in transaminases and the GSG index. Liraglutide is additionally associated with reductions in alanine, phenylalanine, tyrosine and tryptophan, which are indicators of visceral obesity.
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Lack of mitochondrial medium chain acyl-coenzyme A synthetase Acsm3 in an inbred rat strain with diet-induced hypertriglyceridemia and insulin resistance

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Introduction
Metabolic syndrome (MetS), the combination of obesity, glucose metabolism impairment, dyslipidemia and high blood pressure, is becoming a worldwide burden of morbidity and mortality. Both genetic and enviromental factors are involved in its pathogenesis, with heritability of each component of MetS 25–80%.
Aim
We aim to contribute to dissection of the genetic architecture of MetS using PD (polydactylous) rats, which present a unique mix of diet-sensitive MetS with severe hypertriglyceridemia, obesity and insulin resistance but normal blood pressure. In comparison, SHR (spontaneously hypertensive rat) has milder dyslipidemia and insulin resistance combined with hypertension. BN (Brown Norway) represents a strain resistant to MetS development.
Materials and methods
6 months old male rats of inbred strains PD, SHR and BN were fed high-fat diet (HFD, short to long-chain fatty acids (FAs)) for 4 weeks. Morphometric and metabolic parameters were measured and liver transcriptome was determined.
Results
The development of MetS was most striking in PD. Weight gain and adiposity increase was significantly higher in PD compared to both BN and SHR. PD animals also showed hyperinsulinemia and hypertriglyceridemia and impaired glucose tolerance after HFD. Analysis of liver transcriptome showed 941, 875 and 348 deregulated genes comparing PD vs BN, BN vs SHR and PD vs SHR, respectively. In PD, we found lack of *Acsm3* transcript and protein product – mitochondrial enzyme involved in activation of medium chain FAs for beta oxidation. Mitochondrial respiration rate for octanoate in liver homogenates revealed significantly lower oxygen consumption in PD compared to SHR rats. In addition, Acsm3 absence in PD rats was associated with about 100 times increase in hepatic stearoyl-CoA desaturase 1 (Scd1) gene expression.
Conclusion
Most striking finding in liver transcriptome was absence of *Acsm3* expression in PD rats. Since the gene is coding for an enzyme activating medium chain FAs, we suppose it could play a role in development of MetS in PD. This hypothesis is supported by the observed reduced mitochondrial octanoate respiration in liver homogenates and increased Scd1 expression. We found no causal mutation in *Acsm3*coding sequence, introns and core promoter, which could explain the absence of mRNA. To elucidate role of A*csm3*in MetS pathogenesis, a transgenic rescue of *Acsm3* in PD is underway.

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Evaluation of serum and salivary subfatin and asprosin hormone levels in patients with nonalcoholic steatohepatisis

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Objective
Nonalcoholic steatohepatitis (NASH) is a metabolic disease characterized by liver steatosis. There is a correlation between liver steatosis and metabolic hormone dysregulation. Subfatin and asprosin are two important metabolic components of adipose tissue and play a role in carbohydrate metabolism, insulin resistance, and glucose regulation. Therefore, the primary aims of this study were to determine how serum and salivary subfatin and asprosin levels change simultaneously in samples obtained from patients with NASH; to compare these levels with those in control cases; and to determine whether there is any correlation of these levels with other metabolic parameters, such as high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL).
Materials and methods
Ninety-seven patients with NASH with a previous histopathological diagnosis and 30 healthy volunteers with no known disease (control group) were included in the study. The patients were classified under four stages: stage 1 ($n=30$), stage 2 ($n=30$), stage 3 ($n=22$), and stage 4 ($n=15$); 5 cc blood and 1 cc saliva were collected from the patients. Subfatin and asprosin levels in biological samples were studied using ELISA method. Other biochemical parameters (FBS, Hba1C, LDL, HDL, total cholesterol, triglyceride, AST, ALT, insulin, urea, creatinine, and uric acid) were studied using autoanalyzers.
Results
The median age and BMI of obese patients were significantly higher in the patient group than in the control group ($P<0.05$). Hba1C and glucose, insulin, LDL, total cholesterol, triglyceride, AST, ALT, urea, and uric acid levels were significantly higher and HDL levels were significantly lower in the patient group than in the control group ($P<0.05$). Serum and salivary asprosin levels of the patient group were significantly lower than those of the control group ($P<0.05$). Serum and salivary subfatin levels were lower in the patient group than in the control group; however, the difference was not significant ($P>0.05$).
Conclusion
On the basis of the study results, we concluded that subfatin and asprosin levels are lower in patients with NASH than in healthy subjects. In addition to serum, subfatin and asprosin are present in saliva. Both blood and saliva are thought to be the sources of subfatin and asprosin in saliva. Therefore, subfatin and asprosin are indicators of metabolic events (including NASH), and their presence in the saliva constitutes an important alternative to blood as the collection of saliva is noninvasive.

Keywords: nonalcoholic steatohepatitis, subfatin, asprosin.
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Capabilities of ultrasonography in diagnosis of latent post-injection lipodystrophies

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Introduction
Condition of injected skin and subcutaneous tissue is assessed by visual inspection and palpation and it has only 10–15% diagnostic value. The standard ultrasonography comparison of symmetrical skin areas is not valuable as they are usually used for injections.
Objective
We examined 143 patients, aged 43.3±3.9 years, with DM duration of 6.5±2.8 years, receiving basal-bolus insulin therapy.
Methods
Ultrasonography was performed for 78 volunteers with uninjected skin and subcutaneous tissue of the lumbar and epigastric regions. We determined correction factors that predict skin thickness at the injection site if insulin weren't administered.
Results
Ratio indices at the injection regions were calculated – the ratio of the dermis thickness of the studied to lumbar region. In the anterolateral shoulder region, normal indices were defined: for epidermis in the range of 0.9–1.0; for dermis – 0.5–0.7. In the anterolateral thigh region: for epidermis – 0.8–1.0; for dermis – 0.5–0.8. In the umbilical region: for epidermis – 0.8–1.0; for dermis – 0.6–0.8. In the upper outer quadrant of the buttock: for epidermis – 0.8–1.0; for dermis – 0.7–0.9. With values decrease, hypotrophic lipoatrophy development is expected. When performing ultrasonography and analyzing the ratios of the epidermis and dermis of the lumbar region to injection sites, changes were detected in every 4 (37 patients), which is 25%. Post-injection hypotrophic lipoatrophy was diagnosed in the umbilical region (49%), in the anterolateral shoulder (24%) and thigh (17%) regions, in the gluteal region (10%).

Conclusion
Using ratio indices during ultrasonography, it is possible to diagnose and treat post-injection lipodystrophies in the earliest time in order to achieve the highest insulin injection bioavailability.

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AEP264

Evaluation of glycemia course in patients with diabetes mellitus type

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Objectives
To analyze the indicators of carbohydrate metabolism depending on the characteristics of the manifestation of hypoglycemic reactions.
Materials and methods
The study daily glucose dynamics was carried out with Medtronik MINIMED Continious Glucose Monitoring System (CGMS), USA.
The standard glycose profile (4–5 per day) was measured in capillary blood with the Precision PCχTM glucose meter, MediSense. To analyze the continuous glycemic curve, the risk indices (RIn) of hypoglycemia and hyperglycemia were calculated over the study period.
We have examined 162 patients with diabetes mellitus type 1.
There was group 1 with the presence of hypoglycemic reactions ($n=99$), and group 2 with the absence of hypoglycemic reactions ($n=63$).
The groups are comparable in terms of mean age (28.59±7.10 years), duration of DM type 1 (10.46±7.28 years), and BMI (24.12±3.62 kg/m^2).
Results
in the total number of examined, the median RIn of hyperglycemia was 13.15 [9.00; 20.00], RIn of hypoglycemia was 5.25 [2.00; 9.60], HbA1C level was (9.00% [7.70; 10.60]).
When taking into account the presence of hypoglycemic reactions in the group 1, RIn of hyperglycemia was 11.80 [9.00; 18.30], RIn of hypoglycemia was 8.15 [4.50; 12.90], in group 2, RIn of hyperglycemia was 18 30 [10.20; 24.80], RIn of hypoglycemia was 1.20 [0.25; 3.25].
Assessing RIn of hypo- and hyperglycemia in groups taking into account the severity, in group 1, the high RIn of hypo- and hyperglycemia (76%) prevailed over the low one (RIn of hypoglycemia 10% and RIn of hyperglycemia (8%) $P<0.001$, in group 2 low RIn of hypoglycemia (69%) and high RIn of hyperglycemia (78%) accounted for the majority ($P<0.001$).
Conclusions
In the examined patients with DM type 1, the median RIn of hyperglycemia and RIn of hypoglycemia corresponds to a high risk of developing hyper- and hypoglycemic conditions and indicates decompensation of DM 1.
Decompensation of DM type 1 in patients with hypoglycemic episodes is caused by posthypoglycemic hyperglycemia.

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Hand grip strength is correlated with peripheral neuropathy and metabolic control in patients with diabetes

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Background
Peripheral neuropathy is the most prevalent chronic complication in diabetes and increases the risk of sarcopenia in these patients. Hand grip strength (HGS) measurement is a good predictor for the presence of sarcopenia.
The aim of the study was toevaluate HGS in diabetes patients with and without neuropathy and the clinical and paraclinical parameters that are correlated with HGS.
Methods
We evaluated 102 diabetes patients by clinical examination, Michigan Neuropathy Screening Instrument Questionnaire (MNSI-Q) and laboratory measurements. HGS was measured by grip strength dynamometer.
Results
Mean age was 62.8±8.6 years, 64% were women and mean duration of diabetes was 13.7±8.1 years and 43% of patients were diagnosed with peripheral neuropathy. Patients with peripheral neuropathy had higher duration of diabetes 16.8±8.4 vs 11.4±7.3 years ($P=0.001$) and a lower HGS 24.5±9.7 kg vs 30.3± 13.8 kg ($P=0.06$). Prevalence of peripheral neuropathy was similar in women and men. HGS was similar in women with or without neuropathy but HGS was significantly lower in men with neuropathy 33.3±6.8 kg vs 43±8.3 kg ($P=0.004$). HGS was corelated with glycated hemoglobin in the whole group ($r=–0.283$, $P=0.03$) and was negatively correlated with age ($\beta=–0.601$, $P=0.005$) and MNSI-Q score ($\beta=–0.36$, $P=0.05$) in men but not in women.
Conclusion
HGS is significantly correlated with the presence of peripheral neuropathy in men but not in women. HGS measurementisa very useful and easy to use tool in clinical practice to estimate the risk of sarcopenia in men with neuropathy.

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Association between gestational glycemic profile and delivery with a large for gestational age baby in pregnant women with type 1 diabetes

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Bacground
Hyperglycemia is believed to be the underlying cause for many of the adverse fetal, neonatal, and maternal outcomes in pregnancies complicated by type 1diabetes (T1DM). In particular, the rates of a large for gestational age (LGA) neonates and macrosomia remain high and suggest that hyperglycemia may not be the only driver of fetal overgrowth for women with T1DM.
Aim
Our aim was to assess the association between gestational glycemic profiles [HbA1c, postprandial (PG), fasting (FG), mean (MG) blood glucose]and delivery with a LGA baby in women with T1DM.
Methods
Totally, 321 pregnant women with T1DM were enrolled in the study. Data obtained for home-blood glucose monitoring (seven-point profiles), PG, FG, MG and HbA1c in the late 2nd and 3rd trimesters of pregnancy were analyzed. Gestational age at delivery was 37.2±1.3 weeks and birth weight (BW) was 3 383±358.3 g; in total, 86 (26%) neonates were born LGA. The patients were divided into 2 groups (Gr.): LGA-Gr. – 86 patients and non-LGA-Gr. – 235 patients.
Results
In the late 2nd and 3rd trimesters of pregnancy HbA1c, PG, FG and MG levels were statistically higher in LGA-Gr., than in non-LGA-Gr.: HbA1c (%) – 7.3±1.29 vs 6.2±1.63 ($P<0.001$); PG (mg/dl) – ($P=0.000$); FG (mg/dl) – ($P=0.000$); MG (mg/dl)- ($P=0.000$). Pre-pregnancy body mass index (BMI) was higher in LGA-Gr, than in non-LGA-Gr. (kg/m^2) – 27.5± 0.57 vs 22.9± 0.41 ($P<0.001$). In non-LGA-Gr. correlation between body weight (BW) and PG (r –0.794; $P=0.000$) and BW and pre-pregnancy BMI (r –0.580; $P=0.0076$) was observed, thoughno significant interaction betweeninfants BW and HbA1c, FG and MG was found.
In LGA-Gr. strong correlation between BW and PG (r –0.876; $P=0.000$), BW and HbA1c (r –0.603; $P=0.003$), BW and MG (r –0.611; $P=0.002$), BW and pre-pregnancy BMI (r –0.866; $P=0.001$), and no correlation between BW and FG were observed.
Conclusion
HbA_{1c} is less likely to be able to detect shorter-term glucose variability and does not always predict fetal macrosomia. Maternal postprandial glucose excursions in the late 2nd and 3rd trimesters and pre-pregnancy BMI might be relevant in the development of aLGA baby.

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AEP267

Peculitaries of markers of renal function in patients with Diabetic Kidney Disease depending on C/T polymorphism in the DIO 1 gene

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Introduction
Decrease in thyroid hormones (TH) levels is associated with reduced blood flow to kidneys and decreased glomerular filtration rate (GFR) along with alteration of tubular reabsorption.
Deiodinase type 1 is an enzyme that is active in liver and kidneys and plays an important role in TH metabolism.
The aim of the research was to study the dependence of markers of renal function on C/T polymorphism in the DIO 1 gene in patients with DKD.
Material and methods
The C/T polymorphism in the DIO1 gene was studied in 102 patients with diabetes type 2 (T2DM) complicated by CKD in stage ofmicroalbuminuria and 97 healthy subjects – control group.
To assess the dependence of biochemical markers of renal function on the C/T polymorphism in the DIO 1 gene, the following groups has been formed: 19 patients with CC genotype, 69 – with CT and 14 – with TT genotypes.
Blood sample was analysed for blood urea, serum creatinine, urine test for evaluation of microalbumin, creatinine levels. Albumin/creatinine ratio in urine and GFR by CKD-EPI formula were calculated. To access TH levels free triiodothyronine T_3(fT_3), free thyroxine T_4(fT_4), thyroid stimulating hormone (TSH) were determined.
Results
Disorders of distribution of genotype frequencies contributed by the reduction of CC genotype frequency was revealed in the group of enrolled patients comparing to the control group ($\chi^2=6.8$, $P<0.05$), while there was no significant difference between the frequencies of CT and TT genotypes ($\chi^2=2.4$, $P>0.05$ and $\chi^2=1.2$, $P>0.05$).
Blood urea ($P=0.032$), blood cleatinine ($P=0.035$) levels as well as microalbumin ($P=0.041$) and creatinine content ($P=0.039$) in urine were higher in group with TT genotype than in group with CC genotype.
Creatinine in blood serum ($r=-0.362$, $P<0.05$), microalbumin in urine ($r=-0.416$, $P<0.05$) correlated negatively with the level of fT_3. GFR correlated positively with fT_3 level ($r=0.374$, $P<0.05$) and negatively with fT_4 level ($r=-0.326$, $P<0.05$).
Conclusions
1. C allelehas protective properties against violation of TH metabolism in patients with T2DM.
2. Carriers of Tallele with DKD had significantly worse biochemical indices of renal function, that indicates the dependence of these markers on DIO1 polymorphism.
3. Results of correlation analyses showed the dependence between the levels of TH and biochemical indices of renal function.

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AEP268

Association of the APOEgene polymorphism with diabetic nephropathy

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The protein isoformes that are products of the Apolipoprotein E (*APOB*) gene polymorphism have partially altered biological activity and that may lead to greater susceptibility of the patientsto microvascular complications including Diabetic nephropathy (DN)in patients with the Type 2 diabetes mellitus (T2DM). The aim of this study was to evaluate the association between the allele ε2, ε3, and ε4 of the *APOE* gene, as well as their combination, with the development of DN in patients with T2DM from the North Macedonia. The genotypic and allele frequency of the polymorphisms rs429358 and rs7412 in the *APOE* gene was determined in a group of patients with T2DM (with and without DN), and in the control group healthy subjects. The study is designed as a case-control genetic association study. The samples from 88 patients with T2DM were analyzed, including 57 patients with DN and 31 without DN and 26 healthy controls. The demographic, clinical and laboratory data were analyzed in addition to the genetic profiling of the patients. Genotyping of the *APOE* gene polymorphism resulted in determination of the patient's genotype: ε2/ε2, ε3/ε3, ε4/ε4, ε2/ε3, ε2/ε4 or ε3/ε4, as well as of the alleles: ε2, ε3 or ε4. The results revealed a statistically significant association of the genotype ε2/ε3 ($P=0.016$) and the allele ε2 ($P=0.020$) with the occurrence of DN compared to the other genotypes and alleles. The presence of this genotype increases the chances of DN by 4,24 folds and the relative risk by 1,50 folds. In conclusion, the correlation of the *APOE*gene polymorphism and the development of the DN in patients with T2DM was confirmed indicating that there is a potential applicable value in the prognosis and treatment selection.

Keywords: *APOB*; polymorphisms; Type 2 Diabetes mellitus; Diabetic nephropathy.
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AEP269

Characterizing familial partial lipodystrophy: Baseline data of the BROADEN study

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Introduction
Familial Partial Lipodystrophy (FPLD) is a rare genetic disorder characterized by marked loss of subcutaneous adipose tissue from the extremities and is associated with a variety of metabolic abnormalities. While phenotypic elements of the disorder can vary across genotypes, symptomatic presentation, disease severity, and onset can also vary among individuals with the same disease-causing variant, or even among family members. Due to this variability, and the rarity of the disease, an encompassing patient profile has been challenging to determine. Therefore, we present a detailed phenotypic/genotypic description of the FPLD patients who participated in a Phase 2/3 clinical trial.
Methods
Baseline data from patients with FPLD ($n=40$) participating in a phase 2/3 study of volanesorsen (apo C-III antisense oligonucleotide) were analyzed to provide greater insight into the clinical, genotypic and phenotypic profile of patients with FPLD. Patients were required to have FPLD by genetic, familial or phenotypic criteria, fasting triglycerides ≥ 2.3 mg/dl and confirmed diabetes mellitus by an elevated HgbA1c.
Results
Participants had a median age of 49 years (range 28–68 y), were predominately female ($n=29$, 72.5%), with a 78.4 kg (range 57.8–126.1 kg) median body weight and BMI of 29.8 kg/m^2 (range 21.0–44.2). Sixteen patients had genetically confirmed FPLD, with 12 harboring pathogenic missense variants in *LMNA* and 4 in *PPARG*. Additionally, three patients had variants of uncertain significance in FPLD related genes. No patient had a pathogenic variant in *PLIN1, AKT2* or *CIDEC*. Median fasting triglycerides were 8.6 mmol/l (range 2.4–60.4). Seven patients reported using triglyceride lowering medications (statins, fibrates, omega 3/fish oil). All patients had clinical diabetes mellitus with mean HgbA1C of 8.0% (s.d. 1.4%). Twenty-six patients reported use of insulin or other hypoglycemic medications. Medical history of fatty liver disease was reported by 26 patients and mean baseline hepatic fat fraction was 17.6% (s.d. 7.9%).
Conclusion
We conclude that the majority of the eligible participants for this trial lacked variants in the known FPLD genes. FPLD, type 2, due to *LMNA* variants was the most prevalent subtype of FPLD in our cohort followed by FPLD, type 3 due to *PPARG* variants. Both variant positive and negative patient groups had the hallmark traits of abnormal fat distribution, severely elevated triglycerides, diabetes and elevated HgbA1C, and significant hepatic steatosis. The complex characteristics of this disorder support the need for careful clinical phenotyping of the cases and investigation of the variability in the presentations.

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AEP270

A comparison of the level of appetite, food intake, metabolic hormones, basal metabolic rate and adiposity in normal and short stature children

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The acceleration in linear growth at puberty is attributed to the combined physiological effects of both somatotropic and gonadal axes. In synergy, growth hormone (GH) and gonadal steroids (testosterone (T) and estradiol (E2)) stimulate longitudinal bone growth through direct stimulation of chondrocytes and osteoblast. Nutrition such as sufficient amount of nutrients including calcium, phosphate, sodium, potassium and iron and vitamins like vitamin D, vitamin A and vitamin C play an important role in linear bone growth velocity at puberty in both sexes. Amongst others, the secretion of GH is stimulated by ghrelin through GH secretagogue receptor (GHSR). Ghrelin, secreted by enteroendocrine cells of gastrointestinal tract, stimulates the hunger center in the hypothalamus, increases appetite and plays a role in positive energy balance. The present study was designed to determine the level of appetite and food intake, plasma concentrations of metabolic hormones, ghrelin, leptin, obestatin, GH, prolactin (PRL) and triiodothyronine (T3) and basal metabolic rate (BMR) in normal and short stature boys and girls. The amount of food intake over a period of one week was determined through Child Eating Behavior Questionnaire (CEBQ) in 50 normal and 35 short stature children and the amount of calories, nutrients and vitamins were calculated from the food intake by using available literature for each food item. ELISA was used for analysis of plasma ghrelin, leptin, obestatin and PRL while RIA was used for analysis of plasma GH and T3. BMR was calculated by using the Harris and Benedict Equation (1918) for both boys and girls. Data were analyzed using Student's t test, ANOVA and Pearson correlation r. The results revealed that normal children exhibited increased appetite and food intake as compared to short stature children. Moreover, the concentrations of metabolic hormones T3, GH, PRL, obestatin and BMR were significantly higher in normal children as compared to short stature children indicating lower level of energy balance in short stature children. In contrast, the concentrations of ghrelin were significantly higher in short stature children as compared to normal children suggesting a lack of negative feedback effect on ghrelin secretion. Similarly, the concentrations of leptin were also higher in short stature children indicating greater deposition of fats and higher BMI of short stature children. In conclusion, normal children exhibited increased appetite, food intake and higher concentrations of T3, GH, PRL, obestatin and BMR, whereas short stature children had increased concentrations of ghrelin and leptin and higher adiposity.

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AEP271

MODY5 with a whole deletion of HNF1B based on 17q12 microdeletion in a patient with primary amenorrhoea due to severe genitalabnormalities

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Introduction
Maturity-onset diabetes of the young (MODY) 5 is caused by mutations in the *TCF2 (HNF1B)* gene encoding the transcription factor hepatocyte nuclear factor-1. However, in 60% ofthe patients with a phenotype suggesting MODY5, no pointmutation is detected in *TCF2* gene. In some of those patients genomic rearrangements may be responsible for the phenotype.
MODY5 or renal and diabetes syndrome (OMIM #137920) encompasses a wide clinical spectrum comprising diabetes, pancreas atrophywith subclinical exocrine deficiency, progressive nondiabetic nephropathy, kidney and genital malformations and liver abnormalities.
Case report
We present a case of a 22-year-old woman with primary amenorrhoea and hirsutism. In adolescence due to abnormal liver test she was diagnosed with Gilbert syndrome. During the current diagnostic process imaging findings including ultrasonography and MRI of the abdomen revealed normal vagina and ovaries but rudimentary uterus, bilateral kidney cysts, laboratory test revealed elevation of the serum levels of the liver transaminases, adrenal androgenization (NCCAH was excluded), impaired fasting glucose and impaired glucose tolerance with moderate hyperinsulinemia and hyperuricemia. She was consulted by a geneticist and renal cysts and diabetes syndrome was suspected. The sequencing of *HNF1B* gene was ordered but revealed no mutation, whereas multiplex ligation-dependent probe amplification (MLPA) P297-C1 revealed 17q12 deletion including genes: *LHX1, AATF* and *HNF1B* genes.
Conclusions
In conclusion we hope that our detailed description of the patient with the phenotype of MODY 5/renal cyst and diabetes syndrome due to 17q12 deletion will contribute to the further genotype-phenotype delineation of that syndrome. We would also like tostress that in patients with a phenotype suggesting MODY5 and no pointmutation detected in *HNF1B* gene, genomic rearrangements including deletions should be searched for.

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AEP272

Difficulties in diagnosing of artificial hypoglycemia: Insulin analogues

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Introduction
One of the manifestations of Munchausen syndrome is the deliberate injection of insulin to achieve hypoglycemia or artificial hypoglycemia. If human insulin is injected, we will always determine high level of insulin and low level of Cpeptideatthemomentofhypoglycemia. Incasesof insulin analogues injection the diagnos is maybe difficult when we use analyzers specific only to human insulin: the low level of IRI and C peptide will be determined.
Objectives
Tocomparethediagnosticaccuracyof analyzers AbbottArchitect (AA) andRoche (R) in determining the IRI levelafterinjectionthe insulin analogues.
Methods
120 patients with suspected NDH aged 18–80 wereincludedin a cross-sectional study. According to the results, we selected the patients ($n=14$) with hypoinsulinemic hypoglycemia (glucose less than 2.8 mmol/l, C peptide less than 0,6 ng/ml, IRI less than 3 μU/ml), diagnosed by the R kit. Then we determined the IRI level in the same blood sample using AA kit.
Results
IRIlevelsaccordingtothedataofdifferentanalyzers were different, but in 93% of cases ($n=13$) the differences were not clinically significant; the diagnosis did not changed (hypoinsulinemic hypoglycemia). Onlyinone patient we revealed significant change of IRI level (more than 2000%): 1.91 μU/ml by theR kit and 42 μU/ml by the AA kit. Taking into account the level of Cpeptide lessthan 0.6 ng/mlwe diagnosed the artificial hypoglycemia. In addition, we found the injection marks on the patient body. The patient was referred to a psychiatrist's consultation. The causes of hypoinsulinemic hypoglycemia in the other patients in our study are: non-β-cell tumors, adrenal and hepatic insufficiency.
Conclusion
inthecasesofusingkits, that determine only human IRI, if the deliberate injection of insulin analogues is suspected (hypoinsulinemic hypoglycemia), for the confirmation the diagnosis it is advisable to investigate the same blood samplewith hypoglycemia using kits, that also determine insulin analogues, forexample, the analyzer AA. Duringtheanalyze of the IRI levels it is required to take into account the C peptide value, which will be always low in cases ofdeliberate injection of any insulin.
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AEP273

Effects of different metabolic states and surgical models on glucose metabolism and secretion of ileal L-Cell peptides: Results from the HIPER-1 study

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Objective
To compare the impact of 4 surgical procedures (mini gastric bypass [MGB], sleeve gastrectomy [SG], ileal transposition [IT], and transit bipartition [TB]) versus medical management on gut peptide secretion, beta cell function, and resolution of hyperglycaemia in type 2 diabetes (T2DM).
Research design and methods
A mixed-meal tolerance test (MMTT) was administered 6–24 months after each surgical procedure (mini gastric bypass [MGB], sleeve gastrectomy [SG], ileal transposition [IT], and transit bipartition [TB], $n=30$ in each group) and the result was compared to matched lean ($n=30$) and obese ($n=30$) T2DM participants undergoing medical management
Results
MGB and IT participants had a greater increase in plasma glucose concentration following MMTT than SG and TB participants. MGB participants exhibited the greatest increase in the incremental area under the curve of plasma glucose concentration above baseline (ΔG_{0-120}) ($P<0.0001$). Insulin sensitivity was comparable across surgical groups, and statistically greater in surgical participants than in obese nonsurgical participants ($P<0.0001$). Beta cell responsiveness to glucose was greater in SG and TB than in MGB and IT participants ($P<0.001$) despite a smaller increase in $\Delta GLP\text{-}1_{0-120}$ relative to IT. Postoperative beta cell function was the strongest predictor of hyperglycaemia resolution.
Conclusions
The present study demonstrated that the level of beta cell function after bariatric surgery is the strongest predictor of hyperglycaemia resolution. The study also demonstrates a disconnection between postprandial GLP-1 levels and beta cell function among the studied surgical procedures.

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AEP274

The influence of simultaneous pancreas-kidney transplantation on the evolution of diabetic foot lesions and peripheral arterial disease

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Introduction
Simultaneous pancreas-kidney transplantation remains the best treatment option in type 1 diabetic patients with chronic kidney failure, providing a euglycemic state associated with an improvement on diabetic chronic complications. However, there are only a few studies addressing the potential ischemic deterioration of peripheral arterial disease, due to blood diverting from the iliac artery to the kidney graft.
Aim
Evaluate diabetic foot lesions and peripheral arterial disease evolution in simultaneous pancreas-kidney transplantation recipients and investigate if they are more frequent in ipsilateral lower limb of kidney graft.
Methodology
A retrospective cohort, including patients submitted to simultaneous pancreas-kidney transplantation inour tertiary center, between 2000 and 2017. Diabetic foot lesions and peripheral arterial disease frequencies were evaluated and then compared in the period before and after transplantation.
Results
Two-hundred and eleven patients were included, being 50.2% ($n=106$) female, with a median age at transplantationof 35 years. The median time since diabetes diagnosis was 23 years. The median time under dialysis was 22 months, 68.2% ($n=144$) undergoing hemodialysis. The mean HbA1c before the transplantation was $8.6\pm1.6\%$ and the most recent median was 5.5%. In 2019, the patient, kidney and pancreatic graft survival was 90.5% ($n=191$), 83.4% ($n=176$) and 74.9% ($n=158$), respectively. In the pre-transplant period, 12.3% ($n=26$) had peripheral neuropathy, 2.8% ($n=6$) had peripheral arterial disease and 5.3 ($n=11$) suffered some foot injury. In post-transplant period, 39.3% ($n=83$) had peripheral neuropathy, 17.1% ($n=36$) peripheral arterial disease and 25.6% ($n=54$) developed ulcers, 14 of which in the ipsilateral lower limb of kidney graft, 19 in the contralateral and 21 bilateral (25.9% vs 35.2% vs 38.9%, $P=0.49$). Nine patient (4.3%) underwent major amputation, 2 of the ipsilateral limb, 6 of the contralateral and 1 bilateral (22.2% vs 66.7% vs 11.1%, $P=0.09$).
Conclusion
Despitesimultaneous pancreas-kidney transplantation positive effects on diabetic chronic complications, we verified a high prevalence of peripheral neuropathy and diabetic foot ulcers in our sample. Diabetic foot lesions were not more frequent in the ipsilateral lower limb of kidney graft, reducing the 'steal syndrome' role in these patients.

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AEP275

Female AKR1D1 knockout mice have impaired intestinal health with evidence of gut dybiosis, increased gut permeability and an increased incidence of colon cancer

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Metabolic syndrome (MS) is an important etiologic risk factor for the development and progression of certain cancers, including colorectal. Bile acids (BA) are potent antimicrobials that support gastrointestinal health and the dysregulation of BA homeostasis is thought to contribute to gut dysbiosis and drive endotoxemia. Furthermore, an increase in the cytotoxicity ofintestinal BA species can directly damage enterocytes and promote carcinogenesis. We have previously shown that expression of bile acid synthesis enzyme, 5β-reductase (AKR1D1), is decreased in patients with non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of MS and here we demonstrate the impact of AKR1D1 deletion on gastrointestinal health in C57BL/6 mice. Female and male wildtype (WT) and AKR1D1 knockout (KO) mice were maintained on a control diet until 52-weeks of age. In both sexes, AKR1D1 deletion decreased BA levels and altered composition, as determined by LC-MS/MS analysis, leading to a more cytotoxic BA profile. Although 16s rRNA analysis ofcecal chyme showed no change in total bacterial counts there were family level changes in bacterial composition. Consistent with ileal damage, female AKR1D1KO mice had decreased villi lengthand increased crypt depth. Suggesting increased intestinal permeability and endotoxemia the expression of the tight junction genes *Claudin 1*, *ZO-1* and *Occludin* were reduced and the presence of bacterial DNA in the liver increased, as was hepatic mRNA and protein levels of TLR4 along with expression of TLR4 mediated genes, *Nfkb1* and *Tnfa*. In the colon female AKR1D1 KO mice had decreased crypt depth and greater numbers of cells stained for the proliferation marker Ki-67. Furthermore, there was increased incidence of abnormal growths (tumours and polyps) in the proximal colon; 20% of female AKR1D1 KO mice compared to 0% of WT. Interestingly, male AKR1D1 KO mice had a much milder intestinal phenotype with decreasedexpression of *Claudin 1*, *ZO-1* and *Occludin* but without signs of damage in the ileum or colon or of endotoxemia in the liver. No abnormal growths were found in either WT or AKR1D1 KO male mice. Collectively, our results suggest that reduced AKR1D1 activity, as that seen in patients with NAFLD, has a sex specific impact on intestinal health, driving intestinal damage and gut permeability and potentially contributing to the risk of colon cancer in females.

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AEP276

Metabolic and cardiovascular consequences of Ramadan fasting in type 2 diabetic patients

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Introduction
Ramadan fasting stands for abstaining from eating, drinking, smoking and oral medication use from predawn to sunset during one month. The duration of the fast from 10 to 19 hours, lifestyle changes and sleep disturbances can affect the glycemic control in diabetic patients with a high risk of hypoglycemia and hyperglycemia. However, fasting has been shown to improve insulin sensitivity and reduce oxidative stress, inflammation and the risk of atherosclerosis.
The objective of our study was to assess the impact of fasting on metabolic and cardiovascular profile in type 2 diabetic patients.
Methods
We conducted a prospective case-crossover observational study including 47 type 2 diabetic patients treated with metformin and / or sulphonylurea, with an HbA1c < 10% and who intended to fast the month of Ramadan 2019, in the absence of a major contraindications. Clinical and biological parameters were evaluated before (T0) and after the month of Ramadan (T1). Cardiovascular risk was estimated using the Framingham score.
Results
Study population included 26 women and 21 men with a mean age of 54.5 ± 10.3 years. The mean level of HbA1c before the month of Ramadan was 6.9 ± 0.9%. The number of days of fasting was 29.25 ± 2.31 days. The prevalence of hypoglycemia symptoms was 15%. No severe complications were recorded. During Ramadan fasting, dietary intake decreased by 19%. At T1, a weight loss was observed in 70% of cases with a significant reduction in weight ($P=0.004$), body mass index ($P=0.005$) and waist circumference ($P=0.02$). However, changes in blood pressure, fasting blood glucose, fructosamine level, total-cholesterol, triglycerides, HDLc, LDLc, uric acid and HOMA-IR index were not significant. There were a decrease in high-sensitivity CRP level ($P=0.05$) and in fibrinogen level ($P=0.005$). A decrease in Framingham score occurred in 35% of participants with a decline of 5.9 ± 3.6%.
Conclusion
Ramadan fasting reduced the cardiovascular risk in type 2 diabetics, essentially through an improvement in the inflammatory and anthropometric status. Moreover, favorable changes in lipid profile and blood pressure were not significant in our study.

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AEP277

Association and predictive ability of maternal body composition parameters in early pregnancy to identify gestational diabetes mellitus

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Background
Accurate early risk prediction for gestational diabetes mellitus (GDM) would target intervention and prevention in women at the highest risk. We evaluated maternal risk factors and parameters of body composition to develop a prediction model for GDM in early gestation.
Methods
A prospective observational study was undertaken. Pregnant women aged between 18–50 y of age with gestational age between 10–16 weeks were included in the study. Women aged ≤18 y, twin-pregnancies, known foetal anomaly or pre-existing condition affecting oedema status were excluded. 8-point skinfold thickness, MUAC, waist, hip, weight and ultrasound measurements of subcutaneous (SAT) and visceral abdominal adipose (VAT) were measured. Oral glucose tolerance test (OGTT) for GDM diagnosis was undertaken at 30w gestation. Binomial logistic regression models were used to predict GDM. ROC analysis determined discrimination and concordance of model and individual variables.
Results
188 women underwent OGTT at 30 w gestation. 20 women developed GDM. BMI (24.7 kg.m^2 (±6.1), 29.9 kg.m^{-2} (±7.8), $P=.022$), abdominal SAT (1.32 cm (CI 1.31–1.53),1.99 cm (CI 1.64–2.31), $P=.027$), abdominal VAT (.78 cm (CI .8–.96), 1.41 cm (CI 1.11–1.65), $P=.002$), truncal SFT (84.8 mm (CI 88.2–101.6), 130.4 mm (CI 105.1–140.1), $P=.010$), waist (79.8 cm (CI 80.3–84.1), 90.3 cm (CI 85.9–96.2), $P=.006$) and gluteal hip (94.3 cm (93.9-98.0), 108.6 cm (99.9–111.6), $P=.023$) were higher in GDM vs non-GDM. After screening variables for inclusion into the multivariate model, family history of diabetes, previous perinatal death, overall insulin resistant condition, abdominal SAT and VAT, 8-point SFT, MUAC and weight were included. The combined multivariate prediction model achieved an excellent level of discrimination, with an AUC of 0.860 (CI 0.774–0.945) for GDM.
Conclusions
An early gestation risk prediction model, which incorporates known risk factors, and parameters of body composition accurately identify pregnant women in their first trimester who developed GDM later on in gestation. This methodology could be used clinically to identify at risk pregnancies, and target specific treatment through referred services to those mothers who would most benefit.

Table 1 Concordance statistic (AUC) for all variables computed with receiver-operator curves(ROC) analyses for GDM, in order of descending AUC value ($n=16$).

Predictive variable	AUC	95% CI	*p*-value
VAT	0.743	.628–.858	<0.0005**
Σ SAT & VAT	0.739	.618–.860	<0.0005**
Truncal SFT	0.730	.613–.846	0.002**
Subscapular SFT	0.728	.607–.848	0.002**
Supraspinale SFT	0.726	.612–.839	0.002**
Abdominal SFT	0.722	.605–.839	0.003**
SAT	0.713	.58–.839	0.002**
Σ 8-points SFT	0.710	.589–.839	0.005**
Waist	0.705	.570–.841	0.004**
Hip	0.701	.564–.838	0.005**
Supra-iliac SFT	0.699	.585–.814	0.007**
Thigh SFT	0.681	.564–.799	0.014*
Weight	0.676	.537–.815	0.015*
Appendicular SFT	0.673	.552–.794	0.019*
BMI	0.670	.535–.806	0.018*
Bicep SFT	0.667	.523–.811	0.024*
Tricep SFT	0.646	.514–.778	0.049*
MUAC	0.639	.496–.781	0.055
Calf SFT	0.637	.501–.773	0.064

*= statistically significant at $P \leq 0.05$, **= statistically significant at $P \leq 0.01$.

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AEP278

Glucose metabolism and lipid profile in centenarians: What can they predict?

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Aim of the study
To assess the most important metabolic factors in centenarians and their impact on mortality and prognosis
Materials and Methods
Itwasalongitudinalstudy, including 82 centenarians (95 years and older), who live in Moscow. Complex geriatric assessment and blood tests were performed. Complex geriatric assessment included past medical history, FRAIL, IADL-C, MNA, GDS-15 and MOCA scores. We also analyzed levels of HbA1c, cholesterol, LDL, HDL. QoL questionnaires were used as well. In one year after the investigations we contacted patients' relatives or social workers to find out about patients' status. The statistical analysis was performed usingIBM SPSS Statistics package Version 26. Statistically significant were differences with $P<0.05$.
Results
Mean age of the patients was 98,3 [±1.9] years, while 87.8% of the cohort were women. Analyzing functional status we found out that 34,4% of the patients were frail, and the number of prefrail patients was 56,2%. Cognitive impairments of different severity were presented in 84,4% of the patients. The median lipids valueswere as follows: total cholesterol – 4,8 [4.2;5.8], triglycerides – 0.97 [0.8; 1.2], HDL – 1.3 [4.2; 5.8), LDL – 3,1 [2.6; 3.7], HbA1c –5.8 [5.6; 6.1]. In 59% of the patients HbA1c was below 6%; 33% had concentrations between 6% and 6.4%, and only in 8% we found HbA1c higher than 6.5%. None of the patients received any sugar-lowering therapy and only 2 (3.2%) were previouslydiagnosed with diabetes. No correlation was also found between HbA1c values and lipids profile. After dividing patients into subgroups depending on stage of carbohydrate metabolism disorders we did not notice any statistically significant differences in lipid profile in them ($P=0.005$). Comparing survivors and non-survivors groups we did not find any significant differences in total cholesterol, LDL, HDL and HbA1c ($P<0.005$). While comparing functional status and QoL with metabolic profile we discovered positive correlation ($r=.834$) between total cholesterol and index of instrumental activity, and between LDL and IADL as well as MNA score ($r=.732$ and .634 respectively).
Conclusion
In centenarians usual prognostic factors such as HbA1c and lipids do not have any impact on survivalbut they influence functional status and QoL. Further investigations of metabolic status in super old personsare needed to personalize their lifestyle and treatment goals.

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AEP279

Association of FT3 levels and FT3/FT4 ratio in the first trimester with the risk of developing gestational diabetes

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Introduction
Gestational diabetes (GD) is one of the most common complications of pregnancy. Thyroid hormones play an important role in carbohydrate homeostasis, however, their influence on the risk of developing gestational diabetes has shown contradictory results.
Objective
To explore whether variations in thyroid function parameters, within the thresholds of normality, can be associated with the risk of developing GD.
Material and Methods
In a case-control study, 107 pregnant women (37 cases and 70 controls) matched according to age, BMI and previous pregnancies, from a sufficient iodine population and with normal thyroid function were included. TSH, fT4 and fT3 and the fT3/fT4 ratio were assessed in the first (week 10–12) and second (week 24–28) trimester of pregnancy. Biomarker levels were categorized into tertiles and the odds ratio (OR) for gestational diabetes was calculated as a measure of association with their 95% CI.
Results
Mean age was 33.24±5.1 years in cases and 32.97±4.5 years in controls ($P=0.779$). There were also no significant differences between the groups in their BMI, smoking habits, presence of antithyroid antibodies, use of iodized salt or iodized supplements. Of the parameters analyzed, only the fT3: 3.10±0.27 vs 2.86±0.25 ($P<0.05$) and the fT3/fT4 ratio: 2.94±0.35 vs 2.67±0.29 ($P<0.05$) in the first trimester showed significantly different values between cases and controls. Patients with fT3 and fT3/fT4 levels in the higher tertile presented a higher risk of GD than pregnant women in the lower tertile. The association was: OR 7.50 (2.47–22.69) and OR 4.38 (1.51–12.64) for fT3 and fT3/fT4 ratio respectively. No significant associations were identified in any of the other parameters analyzed.
Conclusions
Our results suggest that pregnant women with the highest levels of fT3 and fT3/fT4 in the first trimester of pregnancy are at increased risk of developing gestational diabetes regardless of traditional risk factors.

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AEP280

Protein Kinase Cα attenuates neuronal insulin signalling and worsen neuronal insulin-resistance

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PKCα has been implicated in different neuronal functions like, apoptosis, synaptic plasticity, and memory formation. PKCα has been linked to control insulin signalling in peripheral tissues as a feedback regulator. However, the exact mechanism how this kinase regulates insulin signalling in neuron is not yet understood completely. Therefore the objective of the present study was to understand the mechanism of action of PKCα on neuronal insulin signalling cascade. Recently we have shown in differentiated Neuro-2a (N2a) cells *in vitro,* that acute phorbol 12-myrisate 13-acetate (PMA), a well-known activator of PKC, (400 nM for 2.5 min) decreased Akt activity because of the activation of PKCα. In order to understand how the Akt activity was decreased, in our present study we have used differentiated N2a cells, treated them with or without chronic PMA (1 μM, 24 hours) (chronic PMA decreases endogenous PKC levels) or acute (400 nM for 2.5 min) PMA, with or without insulin (100 nM, 30 min). The inhibition in Akt activity was reversed and increased by 25% when neuronal cells were treated with chronic PMA, which decreased PKCα levels. This showed that PKCα inhibits insulin signalling pathway through Akt. To test PKCα contribution in insulin-resistance, N2a cells were differentiated in insulin-sensitive (MF) and insulin-resistance (MFI) condition, as reported earlier from our laboratory. Results have demonstrated that PKCα translocated 2.5 fold more in plasma membrane in MFI condition as compared to MF condition. However, when PKCα was inhibited using Go6983 (which blocked PKCα membrane translocation), Akt activity increased by 30% in the plasma membrane of neurons in MF (insulin- sensitive) condition. However, as the translocation of PKCα was more in plasma membrane in MFI (insulin resistant) condition, Akt activity was reduced in the plasma membrane in MFI condition. These data together demonstrated that PKCα negatively regulates insulin signalling in insulin-sensitive neurons and even worsen the signalling in insulin resistant N2a cells. Further studies are required to elucidate the role of PKCα in neuronal insulin signalling and insulin-resistance.

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AEP281

The MAFA gene mutation responsible for familial insulinomatosis and diabetes impairs insulin secretion and results in downregulation of critical cell cycle regulators

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The islet-enriched transcription factor MAFA regulates the expression of genes critical to beta cell function and insulin secretion. We previously described anovel *MAFA* mutation (c.191C>T, p.S64F) causing familial insulinomatosis and diabetes mellitus, with male carriers more often developing diabetes and females more prone to insulinomatosis. The exact molecular mechanisms underlying these phenotypes are unclear. In this study, we assessed glucose metabolism and beta cell function in *MAFA*mutationcarriers and studied the effects of the S64F mutation in a beta cell line. Six seemingly unaffected carriers (3M, 3F) underwent oral glucose tolerance (oGTT) and mixed meal tolerance (MMTT) tests. Glucose, insulin, C-peptide, active GLP-1, GIP and glucagon were measured and results were compared to age-, BMI- and gender-matched healthy controls. Insulin secretion, cell viability, apoptosis and the transcriptome profile were investigated in INS-1 cells stably transduced with wild-type (WT) and S64F human MAFA.
The oGTT results were in keeping with diabetes or impaired glucose tolerance in five of the six carriers. During the oGTT and MMTT, glucose levels were increased in both male and female carriers compared to healthy controls, although males were more markedly hyperglycaemic. Insulin and C-peptide levels were reduced in male carriers while females showed higher insulin and C-peptide compared to controls. The insulinogenic index was reduced only in males, while females had higher HOMA-IR and lower Matsuda index suggesting insulin resistance. Active GLP-1 levels were significantly increased, while glucagon levels failed to suppress during the oGTT in *MAFA* mutation carriers.
In vitro, insulin secretion in response to glucose was significantly reduced in S64F-MAFA INS-1 compared to WT cells. S64F-MAFA cells were also more susceptible to apoptosis compared to WT. RNA-sequencing showed significant negative enrichment of genes involved with cell cycle regulation, cell division, DNA synthesis and repair in S64F cells. These include the transcription factor *Foxm1*, the centromere protein A-encoding *Cenpa* gene and several cyclins (*Ccnd1*, *Ccnd2*, *Ccne1* and *Ccna2)* and cyclin-dependent kinases (*Cdk1*, *Cdk14* and *Cdk18*). Among previously identified MAFA-regulated genes, *Ins2*, *Glp1r* and *Kcnj11* were also downregulated in S64F-MAFA cells.
The S64F *MAFA* mutation leads to impaired insulin secretion and increased susceptibility of beta cells to apoptosis secondary to downregulation of genes involved in glucose-stimulated insulin secretion and cell cycle regulation. These findings likely underlie the hyperglycaemic phenotype and reduced insulin secretion observed in males. However, the mechanisms causing hyperinsulinism in female carriers remain to be elucidated.

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AEP282

Residual fasting C-peptide secretion and its association with glycemic control in type 1 diabetes

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Background
Residual C-peptide (CP) secretion has been associated with better glycemic control in patients with type 1 diabetes (T1D).
Aim
To evaluate how residual fasting CP (fCP) secretion impacts glycemic control in T1D and to identify possible confounding factors.
Methods
A retrospective analysis of adult patients with T1D followed in our department that had their fCP and glucose levels obtained on the same blood sample during the year 2019. Patients with glucose <70 mg/dl were excluded. fCP <0.2 ng/ml was considered as an indicator of absolute insulin deficiency.
Results
98 patients were included:69 (70.4%) with fCP <0.2 ng/ml and 29 (29.6%) with fCP ≥0.2 ng/ml. Patients with fCP ≥0.2 ng/ml had higher age at diagnosis (35.6±10.0 vs 21.8±12.0 year-old; $P<.001$); all of them were diagnosed after 18 years of age (vs 53.6% in the group with fCP <0.2 ng/ml). This group also had fewer patients on functional insulin therapy (FIT) (20.7% vs 42%; $P<.001$), lower daily doses of insulin (0.5±0.2 vs 0.6±0.2 UI/kg/day; $P=.040$) and higher HbA1c variation in the last 2 years(1.7±1.3% vs 1.0±0.6%; $P=.001$). No differences were observed when comparing this groupwith fCP <0,2 ng/ml group in terms of disease's duration, current HbA1c, median HbA1c in the last 2 years and current BMI. In the subgroup of patients using FIT, the ones with fCP ≥0,2 ng/ml had lower current HbA1c (7.0±0.5% vs 7.9±0.9%; $P=.005$); no differences were observed when comparing with fCP <0.2 ng/ml patients in terms of disease's duration, daily insulin dose (UI/Kg/day) and HbA1c variation in the last 2 years. In the subgroup of patients not on FIT, the ones with fCP ≥0,2 ng/ml had higher medianHbA1c (8.7±2,2 vs 7.8±0.8%; $P=.033$) and HbA1c variation in the last 2 years (1.9±1.4 vs 1.9±0.7%; $P=.002$); no differences were observed when comparing with fCP <0.2 ng/ml patients in terms of disease's duration and daily insulin dose. In adjusted multivariate analysis, higher age at diagnosis was an independent predictor of fCP ≥0.2 ng/ml (ORa 1.091; $P=.012$).
Conclusions
Our findings suggest that patients with fCP ≥0.2 ng/ml doing FIT have better glycemic control than the ones with FIT and fCP <0.2 ng/ml. Nevertheless, that association was not found in patients with fCP ≥0.2 ng/ml without FIT. Thus, the potential benefit of persistent CP secretion seems to be dependent on the therapeutic scheme instituted. Additionally, it has been shown that higher age at diagnosis was a predictor for long-term fCP secretion. Therefore, we should try to implement FIT in all patients, although higher age at diagnosis might have the most potential advantage.

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AEP283

Identification of a diagnostic and prognostic miRNA signature in women with gestational diabetes mellitus

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Gestational Diabetes Mellitus (GDM) is characterized by insulin resistance accompanied byreduced beta-cell compensation to increased insulin demand, typically observed in the secondand third trimester and associated with adverse pregnancy outcomes. There is a need for abiomarker that can accurately diagnose GDM, predict onset and accurately monitor status, reducing foetal-maternal morbidity and mortality risks. To this end, circulating microRNAs(miRNAs) present themselves as promising candidates, stably expressed in serum and knownto play crucial roles in regulation of glucose metabolism. We analyzed circulating miRNAprofiles in a cohort of GDM patients ($n=31$) and nondiabetic controls ($n=29$) during the thirdtrimester for miRNA associated with insulin-secretory defects and glucose homeostasis. Weidentified miR-330-3p as being significantly upregulated in GDM compared to nondiabeticcontrols. Furthermore, increased levels of miR-330-3p were associated with better responseto treatment (diet vs insulin), with lower levels associated with exogenous insulin requirement. We observed miR-330-3p to be significantly related to the percentage of caesarean deliveries, with miR-330-3p expression significantly higher in spontaneously delivered GDM patients. These results suggest miR-330-3p may help direct personalized therapy in GDM, predictdiabetic outcome and/or severity and progression, and further discriminate the diagnosticcriteria employed in GDM diagnosis during pregnancy.

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AEP284

Inflammasome components and food addiction behaviors in morbid obesity and bariatric surgery: Novel promising targets for a chronic disease

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Obesity is a chronic metabolic disease associated with important metabolic and inflammatory comorbidities, which can be reversed or improved after bariatric-surgery (BS). However, some underlying mechanisms, independent of weight-loss, are still unknown. In this context, dysregulations in the inflammasome, a multiproteic complex that promotes cytokine maturation and induces cellular pyroptosis, has been associated to the development/stage of some cancer-types and obesity. However, whether the dysregulation in the expression ofinflammasomecomponents is associated to morbid-obesity, BS, the modification of patient´ personal/environmental-behaviors, as well as to comorbidities reversal has not been yet explored. Therefore, the aim of this study was to determine the presence of addictive food behaviors (AFB) in obese patients undergoing BS, evaluate the changes in inflammasome components after BS, and analyze their causal relationships with the reversal of metabolic comorbidities. To that end, we took advantage of the emerging evidenceshowing that gene expression pattern of peripheral blood mononuclearcells (PBMCs) commonly reflects and accompany disease-characteristic expression patterns, and may thus serve as ageneral sentinel, biosensor and early indicator of the instaurationof metabolic disease to analyze the inflammasome components and associated inflammatory factors (n=45; using a qPCR array based on Fluidigm technology) in the PBMCs of 22 patients before and 6-months after BS. Epidemiological/clinical/biochemical variables of the patients were recorded. AFB symptoms (evaluated using the Yale test) were observed in 18100% of patients. An overall dysregulation in inflammasome components, especially NOD-like receptors and cell-cycle and DNA-damage regulators, was observed in patients after BS. Interestingly, the molecular fingerprint of some inflammasome components (i.e. CXCL3/CCL8/TLR4/NLRC4/NLRP12) was able to perfectly discriminate between pre- and post-operative patients. Moreover, some alterations in the inflammasome were associated to certain basal metabolic comorbidities, including type-2 diabetes (CCL2/CXCR1/SIRT1), high blood pressure (AIM2/ASC/P2RX7) and dyslipidemia (CXCL3/NLRP7), as well as to the reversal of metabolic comorbidities after BS (IL18/NLRP12). Remarkably, the alteration in the inflammasome molecular profile after BS (especially cytokine/inflammation/apoptosis-related components) was also associated to some AFB. All these changes were independent of the surgical technique used. Altogether, BS induces a drastic alteration in the expression profile of inflammasome components of PBMCs, which is also modulated by personal/environmental behaviors. Moreover, the inflammasome molecular profile is associated to the presence and reversal of relevant metabolic comorbidities, suggesting that some inflammasome components might be used as novel diagnostic and therapeutic targets in morbid-obesity.

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AEP285

Secretion of bile acids in different techniques of bariatric surgery

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Background

Bariatric surgery (BS) has proven to be an effective and sustainable long-term treatment in the remission of metabolic disorders. Bile acids (BAs) are involved in the improvement of metabolic comorbidities by acting on the distal ileum (releasing GLP1, PYY and FGF19) and on the microbiota. Our aim is to verify whether the formation of ABs depends on the type of bariatric surgery.

Subjects and Methods

21 patients (81% women) underwent bariatric surgery (BS); 9 patients were selected to Roux-en-Y gastric bypass (YRGB) and 12 to Biliopancreatic-diversion (BPD, type SADIS). The patients (with informed consent) were given a mixed meal test before (T1) and after 1 year post BS (T2), collecting samples at times 0-30-60-90-120 min for 15 fractions of ABs, conjugated and unconjugated forms (determined using a UPLC-tandem MS]. Statistics: descriptive mean±s.d. or median (IQR), area under curve (AUC) with non-parametric comparisons. Registry ISCRT81954082.

Results

Mean age: 50.2 (IQR: 43,354,5) y/o; BMI: 43.09±5.80 kg/m^2 in YRGB group vs 48.4±5.27 kg/m^2 SADI-S group. Type-2 diabetes mellitus was present in 56% and 58%, respectively. Total weight loss at one-year was 38.5% (IQR:27.9–44.9) for YRGB and 39.5% (31.4–42.4) in SADIS subjects. Both total and conjugate baseline ABs increased significantly at one year of follow-up (T2). Although BAs increased twice as much after BPD as with YRGB, there were no significant differences between the two surgical techniques. Glycine conjugated BAs (glycocolic, Glycodeoxycholic, and Glycoqueneoxycholic) were the most prominent. (see table). The increase of total postprandial BAs measured by AUC was also significantly increased at one year in both techniques (YRGB: 174.95 T1 vs 416.28 T2; SADI-S 226.08 T1 vs 386.60 T2; P<0.05)

Table 1 Bile acids values according type of bariatric surgery and time point.

	YRGB			SADIS		
	T1	T2	P	T1	T2	P
TOTAL BAs (mg/l)	0.873	1.666	P=0.038	1.049	3.467	P=0.003
CONJUGATED BAs (mg/l)	0.236	1.004	P=0.028	0.431	2.581	P=0.005
UNCONJUGATED BAs (mg/l)	0.651	0.543	P=0.3	0.624	0.744	P=0.158

Conclusions

BAs are increased after one year of bariatric surgery, regardless of the bariatric technique, in particular glycine conjugated forms that are dependent on intestinal microbiota and may play a prominent role in the remission of metabolic comorbidities.

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AEP286

Liraglutide and PYY$_{3–36}$ combination therapy partially achieves the metabolic benefits of Roux-en-Y gastric bypass surgery in diet-induced obese rats

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Background

Circulating levels of the appetite-suppressing and glucoregulatory gut hormones glucagon-like peptide 1 (GLP-1) and peptide tyrosine tyrosine 3–36 (PYY$_{3–36}$) are markedly increased after Roux-en-Y gastric bypass surgery (RYGB), which may contribute to some of its profound metabolic benefits in morbidly obese individuals.

Objectives

To directly compare the metabolic effects of chronic systemic administration of the clinically approved GLP-1 analogue liraglutide in combination with PYY$_{3–36}$ to RYGB in a standardized and controlled setting.

Methods

High-fat diet-induced obese male Wistar rats (n=58) were randomized into 6 treatment groups: RYGB (n=15), sham-operation (n=13), liraglutide subcutaneous (s.c.; 0.4 mg/kg/day)+saline mini-pump (n=5), PYY$_{3–36}$ mini-pump (1 mg/kg/day)+saline s.c. (n=5), liraglutide+PYY$_{3–36}$ (n=11), saline s.c.+mini-pump (n=9). At the start of interventions, animals were given simultaneous free access to high-fat and low-fat diets ad libitum, high-fat food preference and body weight were measured at regular intervals. Open field (OF) and elevated plus maze (EPM) tests were performed about 4 weeks after intervention. Terminal blood samples were collected for biochemical analysis.

Results

Post intervention, the RYGB group lost maximally 8.6±2.9% body weight, while the sham treated animals gained weight continuously. Compared to sham, the bodyweight of RYGB treated animals was about 20% less in the end of the observation period. The PYY+liraglutide and liraglutide only group lost maximally 7.7±3.2% and 5.5±2.4%, whereas the saline and PYY only group gained weight continuously. PYY+liraglutide treated animals were maximally about 17%, liraglutide only treated animals about 13.5% lighter than saline treated animals. Food intake largely followed the same pattern with the RYGB group consuming the least food followed by the liraglutide+PYY$_{3–36}$ group and then by the liraglutide group. Only RYGB treated animals showed a significantly reduced preference for 60% fat diet

compared to sham treated animals in the observation period. PYY+liraglutide or RYGB led to no clear differences regarding the behavior in OF or EPM compared to saline or sham.
Conclusions
Liraglutide and PYY_{3-36} combination therapy partially achieves the metabolic benefits of RYGB. Other double or triple gut hormone combination therapies may therefore be required to achieve the full metabolic benefits of RYGB.

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AEP287

The day-to-day variability of insulin sensitivity measured during ogtt in young adult males

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There are a wide range of tests to measure insulin sensitivity. Alternative techniques for estimating insulin sensitivity include measurements made during the oral glucose tolerance test (OGTT). We aimed to describe the weekly intraindividual daily variability of measures of insulin sensitivity indexes (HOMA-IR, QUICKI, Matsuda's insulin sensitivity index (ISIM), Insulinogenic Index, Early C Peptide, Stumvoll's Insulin Sensitivity Index (ISIS), $OGIS_{120}$) and the impact of body composition, physical activity behaviour, and dietary intake, when using OGTT. Twenty-six healthy, weight stable, young males that visited QUT on 3 occasions over a 3-week period, completed the study. At 1-wk participants had a DXA scan to assess body composition, and received an accelerometer (ActiGraph- GT3X) which they wore during 14 days. Over the next 2-wks, participants undertaken repeated OGTTs, scheduled 7 days apart. Glucose, insulin and C-peptide were measured to assess each participant insulin sensitivity using OGTT at 0, 30, 60, 90 and 120 minutes. Dietary interviews were conducted by phone during a 3-week period, using a multiple-day, multiple-pass, 24-h recall and dietary intakes were assessed using FoodWorks 7 software. Despite of being one of the simplest and largely used surrogate measures of insulin sensitivity, the dailyvariability for HOMA (CV32%) was markedly higher compared with QUICKI (CV5%). The lowest variability was demonstrated by the ISIS (CV2%) and the highest reproducibility (ICC.927). The OGIS 120 also showed a low variability (CV4%). The fat trunk % was negative correlated with fasting insulin ($r=-.433$, $P<.05$), confirming relationship between abdominal fat, hyperinsulinemia and the clinical risk of diabetes. Significant correlation was found between OGIS120 and the length of vigorous physical activity spent a day ($r=573$, $P=.001$). These findings reinforce that reduction of daily physical activity resulted in negative impact on insulin sensitivity in young healthy men. The $Fiber_{intake}$ had a significant negative correlation between $OGIS_{120\ Day\ 2}$ ($P=0.013$; $r=.478$). However, the $Fiber_{iptake}$ explained only 0.03% of the variance of OGTT by $OGIS_{120\ Day\ 2}$. A significant negative correlation ($P=.013$;$r=-.481$) was observed between percentage of body fat and $Fiber_{intake}$, suggesting higher $Fiber_{intake}$ predicted lower body fatness. In conclusion, the insulin sensitivity evaluation obtained from OGTT in apparently healthy individuals is quite consistent and produced reliable results using ISIS. We suggest the use of QUICKI when only fasting measures are available to measure insulin sensitivity.

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Association between the circadian rhythm and the inhibitory effect of glucocorticoids on browning of adipocytes

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White adipose tissue (WAT) stores excess energy as triglycerides, while brown adipose tissue (BAT) dissipates energy through heat, acting as a defense against cold and obesity and as a positive regulator of metabolic functions. The thermogenic function of BAT is mainly regulated by the mitochondrial uncoupling protein 1 (UCP1) in brown adipocytes. Moreover, it has been shown that chronic exposure to glucocorticoids (GC) or synthetic GC receptor (GR) agonists inhibits the activity of brown adipocytes and browning of WAT. Despite the broad literature on the regulation of BAT function and body temperature, little is known on the mechanisms controlling circadian thermogenic rhythms and, more importantly, how this pattern is affected by GC. Thus, aim of this study was to assess the impact of GC on browning of 3T3-L1 adipocytes and on the association with expression of clock genes. 3T3-L1 adipocytes were transdifferentiated into brown adipocytes, then synchronized by serum shock before mRNA analysis of UCP-1 and clock genes. The increase in UCP-1 mRNA substantiated the transdifferentiation into brown adipocytes. Moreover, clock gene expression analysis confirmed the rhythmic regulation of 3T3-L1 adipocytes after serum shock synchronization, with a peak of mRNA expression at 4 h (indicated as Zeitgeber time 4, ZT4) for *Clock* and *Bmal1* (light phase genes), and a peak at ZT16 for *Rev-erbα* and *Rev-erbβ* (dark phase genes). Administration of the GR-agonist dexamethasone (Dexa) to transdifferentiating adipocytes increased the mRNA expression of brown genes (*UCP-1, Tmem26, CD137 and Cidea*) at ZT16, whereas their levels were reduced at ZT4 and ZT10. These preliminary findings suggest that, depending on the time of the day, treatment with GC may have a different impact on metabolism, such as browning of adipocytes and the metabolic functions of both white and brown adipocytes.

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AEP289

Association of nutritional support with in-hospital mortality in malnourished medical inpatients – a population-based cohort study

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Background
Malnutrition has been associated with increased adverse clinical outcomes and affects a considerable proportion of hospitalized medical patients. While recent evidence from clinical trials revealed a survival benefit from nutritional support, data from a large real-world population is still missing.
Methods
In this population-based cohort study, using a Swiss administrative claims database from January 2012 to December 2017, we created a medical inpatient cohort of malnourished patients and matched patients on nutritional support 1:1 on propensity score. The primary outcome was all-cause in-hospital mortality. Secondary outcomes were length of hospital stay, 30-day all-cause hospital readmission, and discharge to a post-acute care facility. We performed sensitivity analyses by stratification for degree of malnutrition.
Results
After propensity score matching, we identified 56'822 cases in the cohort. Patients receiving nutritional support compared with matched controls had a significantly lower in-hospital mortality (2'178 of 28'411 [7.7%] vs 2'490 of 28'411 [8.8%]; OR 0.86 [95% CI, 0.81 to 0.92], $P<0.001$). Malnourished patients on nutritional support faced a 2.5-day longer hospitalization (95% CI 2.3 to 2.7, $P<0.001$). All-cause 30-day readmission rate was significantly lower in the intervention group (17.2% vs 18.4%; OR 0.92 [95% CI, 0.88 to 0.97], $P<0.001$) but there was no difference in the frequency of discharge to post-acute care facility (45.4% vs 44.9%; OR 1.02 [95% CI, 0.98 to 1.06], $P=0.286$). Sensitivity analyses showed an even more pronounced reduction in risk of in-hospital mortality among patients with severe malnutrition (OR 0.71 [95% CI, 0.61 to 0.83], $P_{\text{for interaction}}=0.009$).
Conclusions
In this large cohort study, nutritional support was associated with a lower risk of in-hospital mortality in direct comparison with malnourished medical patients without nutritional support as treated in routine care. These findings are in line with previous controlled data and will help to inform patients, practitioners and authorities regarding the effectiveness of nutritional support in clinical practice.

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AEP290

Magnesium supplementation and higher magnesium levels in T2DM patients are associated with better glycemic control and higher rates of total and partial remission post-bariatric surgery

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Introduction
Magnesium (Mg) is an essential mineral for human health. Chronic Mg2+ deficiency and low Mg2+ dietary intake have been associated with increased risk of T2DM. Despite the increased risk of T2DM associated with Mg2+ deficiency; T2DM is often accompanied by hypomagnesemia, especially in patients with poorly controlled glycemic profiles.
Bariatric surgery remains the most effective long-term therapy for the management of patients with severe obesity. After surgery, micronutrient deficiencies are one of the most common and compelling problems.
Objective
To analyse the effect of Mg supplementation and serum levels in T2DM metabolic parameters and remission after bariatric surgery.
Methods
We performed a cross-sectional study of obese patients who underwent bariatric surgery. Data was assessed preoperatively and one-year after surgery. T2DM was defined as fasting plasma glucose (FPG) ≥126 mg/dl, glycated haemoglobin (HbA1c) ≥6.5%, 2-h plasma glucose after a 75-g oral glucose tolerance test ≥200 mg/dl or the use of anti-diabetic medication (ADM). Complete T2DM remission was defined as HbA1C < 6.0% and no ADM use and partial T2DM remission was defined as HbA1C < 6.5% and no ADM use.
Results
Of a total of 2241 patients submitted to bariatric surgery, we included 644 patients with T2DM. At baseline, 39% of the patients ($n=251$) had Mg deficiency and only 4% of them were on Mg supplementation. Patients with Mg deficiency had poorer metabolic control (HbA1c, FPG, insulin, C peptide, HOMA-IR and number of ADM) compared with patients without Mg deficiency with statystical significance for HbA1c (HbA1c = 6.55 ± 1.34 vs HbA1c = 7.17 ± 1.55, $P<0.0001$), FPG (FPG = 112.45 ± 28.28 vs FPG = 122 ± 42.58, $P<0.006$), and number of ADM (ADM = 1.063 ± 0.89 vs ADM = 1.39 ± 1.07, $P<0.0001$). At the first year, 16.1% of patients had complete T2DM remission. It was more common among patients without Mg deficiency ($P<0.001$). Similar to baseline, patients withoug Mg deficiency had better metabolic control with statystical significance.
Conclusion
Mg supplementation and higher serum Mg levels in patients with T2DM-were associated with better metabolic control and higher rates of complete and partial remission at the first year post-surgery.

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AEP291

Nesfatin-1, an appetite-suppressing and anti-obesogenic neuropeptide, is decreased in the human brainstem of obese subjects.

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Background/Aims
Food intake is orchestrated by complex neuronal networksresiding in the forebrain, hypothalamus, and brainstem, via orexigenic and anorexigenic neuropeptides. Nesfatin-1, the amino-terminal fragment of nucleobindin 2, is a potent anorexigenic and anti-obesogenic neuropeptide, with widespread central distribution in rodents. In obese humans, our research group has recently reported reduced nesfatin-1 protein expression in the lateral hypothalamic area, a brain structure involved in appetite and body weight regulation and connected with brainstem feeding centres. In spite of the wealth of data in animals, no information is available about nesfatin-1 localization in the human brainstem. The aim of the present study was to explore nesfatin-1 distribution pattern in human brainstem nuclei as well as the association between nesfatin-1 protein expression and body mass index.
Methods
For this purpose, human brainstemsections from 20 autopsy cases (13 males, seven females; 8 normal weight, 6 overweight, 6 obese) were examined using immunohistochemistry and double immunofluorescence labeling
Results
Intense nesfatin-1 immunoexpression was observed in various brainstem areas, including nuclei involved in energy homeostasis and in autonomic and behavioral functions, such as the nucleus of the solitary tract, dorsal motor nucleus of vagus, area postrema, inferior olive, reticular formation, raphe nuclei, locus coeruleus, parabrachial nuclei, and pontine nuclei, and in Purkinje cellsof the cerebellum. In addition, nesfatin-1 was extensively colocalized with neuropeptide Y and cocaine- and amphetamine-regulated transcript (peptides playing pivotal role in food intake and energy metabolism)in nucleus of the solitary tract, inferior olive, locus coeruleus, and dorsal raphe nucleus. Interestingly, nesfatin-1protein expression was significantly lower in obese than normal weight subjects in nucleus of the solitary tract ($P<0.05$).
Conclusions
These findings provide for the first time neuroanatomical support for the potential role of nesfatin-1 in the human brainstem neuronal network controlling food intake and energy balance. In the nucleus of the solitary tract, an important hub of energy statusintegration and a neural substrate of food reward, altered neurochemistry such as nesfatin-1 deficiency may contribute to dysregulation of homeostatic and/or hedonic feeding behavior and thus to obesity.

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AEP292

Digital evaluation of ketosis and other diabetes emergencies (DEKODE) algorithm: Automated auditing system for diabetic ketoacidosis (DKA) management

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Background
Effective management of diabetic ketoacidosis (DKA) improves clinical outcomes. Regular auditing and performance feedback are key to achieving sustained and significant improvement in the management of DKA. One of the major limitations for maximal impact of an audit is the delay from initiation to results as the latter may not be applicable to the then current practice. In order to overcome this, we created an automated auditing system called Digital Evaluation of Ketosis and Other Diabetes Emergencies (DEKODE). This system identifies DKA episodes based on prescriptions for fixed rate intravenous insulin infusion (FRIII). Here, we retrospectively validated DEKODE system for monitoring DKA management.
Methods
To retrospectively validate DEKODE model, all episodes identified by DEKODE from September 2018 to August 2019 was manually verified for confirmation of diagnosis. DKA duration was defined as the difference in time between FRIII prescription time and end time for DEKODE. For manually collected data, the difference in the time from diagnosisto resolution as per standard criteria was considered as DKA duration. Further, appropriateness of glucose and ketone measurements during entire DKA duration and fluids prescribed in the first 12 hours of diagnosis were compared between the two datasets. The difference between manual and automated data for DKA duration, FRIII appropriateness, hourly glucose and ketone measurements were analysed using Prism v6.0 (Graphpad Inc) and results are presented as mean and standard error of mean (S.E.M.). Difference in frequencies of hypokalemia and hyperkalemia between manual and automated data was analysed by chi-square test.
Results
150 episodes were identified by DEKODE during the study period. Of these, 147 had manually confirmed DKA. There was no significant difference in DKA duration between DEKODE and manual data (mean ± S.E.M., 16.0 ± 1.0 hours; 17.5 ± 0.9 hours; P = ns) respectively. Similarly, there was no difference in FRIII appropriateness (98.3% ± 1.2%; 97.9% ± 1.1%; P = ns), hourly glucose (98.5% ± 2.6%; 105.6% ± 2.5%; P = ns) and ketone measurements (43.3% ± 2.1%; 47.1% ± 2.2%; P = ns) between the two systems. DEKODE

also accurately predicted the frequency of kalaemic complications with no significant difference in the number of patients recorded with hyperkaelema (7/147; 6/150; P=ns) and hypokalaemia (9/147; 9/147; P=ns). However, DEKODE over-predicted proportion of fluids prescribed (96.9%±3.2%; 84.4%±3.1%; P=0.0047).
Conclusion
DEKODE system could reliably predict DKA duration and management. This can help in monitoring DKA management cutting time from collecting data to analysis, thus providing real-time performance results. Further prospective validation is currently underway.

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AEP293

Type 2 diabetes did not show significant risk effect on cerebral aneurysm in Koreans: A single center, cross-sectional study

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Backgrounds
Cerebral aneurysms are a common disease that affects 1–5% of general populations, with an annual rupture risk of 0–1%. Smoking, high blood pressure, diabetes and aging have been considered as risk factors for cerebral aneurysms, but there were few epidemic studies. In this study, we evaluated the risk effect of diabetes on cerebral aneurysm in Korean population.
Methods
We used data from participants who underwent brain MRA and laboratory test for the screening purpose at the Healthcare System Gangnam Center of Seoul National University Hospital between January 2010 and December 2013. Among a total of 18,477 participants, we analyzed 9,235 whose clinical and laboratory data were eligible. Participants with diabetes were 1,350 (14.6%). Cerebral aneurysm was defined as an abnormal focal dilatation of a cerebral arteries with a maximum diameter greater than 3 mm.
Results
Compared the participants without diabetes, those with diabetes have older age, higher proportion of male and smoking, heavier weight, higher blood pressure, and higher levels of fasting glucose, serum cholesterol and CRP. The proportion of participants with cerebral aneurysm were 4.1% in the diabetic group and 3.7% in the non-diabetic group without statistical significance (P=0.523). In logistic regression, old age and lower LDL-cholesterol showed significant risk effects on cerebral aneurysm, but male gender, diabetes, obesity and smoking did not. Multivariate analyses showed corresponding results.
Conclusion
In this study, diabetes was not significant risk factor of risk of cerebral aneurysms. Neither smoking, obesity, nor hypertension were significant risk factors. Of note, we found that the prevalence of cerebral aneurysms decreased as LDL cholesterol levels increased. The lack of association between the traditional risk factors of atherosclerosis and cerebral aneurysm requires further studies.

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AEP294

Fibroblast growth factor 21 (FGF21) in hyper- and hypothyroidism, association with metabolic disturbances

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Background
FGF21 is a critical metabolic regulator with beneficial effects on lipid and glucose metabolism. FGF21 is produced primarily by the liver and stimulates fatty acids oxidation, which prevents hepatic triglycerides accumulation and nonalcoholic fatty liver disease (NALFD). FGF21also increases insulin sensitivity and glucose uptake in adipose tissue. Paradoxically FGF21 is elevated in insulin resistance states e.g. NALFD, obesity and type 2 diabetes. It is not determined if it results from FGF21 resistance or compensatory increased secretion. In animals and *in vitro* studies thyroid hormones increase FGF21 secretion.
Aim
Investigate the association between circulating FGF21 and thyroid hormones, glucose and lipid metabolism in patients with hyper- and hypothyroidism
Methods
57 hyperthyroid patients with Graves disease, 29 hypothyroid patients with autoimmune thyroid disease and 21 healthy controls were included. Additionally, a subset of 13 hyperthyroid patients was analyzed before, and after radioiodine treatment, in three different thyroid statuses typically occurring in this group – hyperthyroidism, hypothyroidism, and euthyroidism after l-thyroxin treatment. Serum FGF21 was measured with immunoassay.
Rresults
Serum FGF21 levels did not differ significantly in hyperthyroid and hypothyroid patients as compared with healthy subjects [median 100.30 (interquartile range, 59.61–191.93) and 141.50 (66.80–247.40) vs 78.50 (54.00–11.90) pg/ml P=0.196 and 0.058 respectively]. In hyperthyroid patients treated with radioiodine, serum FGF21 level did not change in hyperthyroidism as compared with euthyroidism and hypothyroidism, however it has increased dramatically in hypothyroid phase compared with euthyroidism stage [102.30 (51.4–153.70) vs 199.30 (131.70–266) vs 70.80 (21.80–187.90) pg/ml, P=0.999, P=0.080 and P=0.018 respectively]. In hyperthyroidism, there was no significant correlation between FGF21 serum levels and thyroid hormones, lipids, and glucose metabolism. In rapid onset hypothyroidism after radioiodine treatment, increased FGF21 serum levels correlated positively with triglycerides and cholesterol (Spearman coefficient rs=0.46 and rs=0.36 respectively) and correlated inversely with fT4 and SHBG (rs=–0.34 and rs=–0.41 respectively). In euthyroidism FGF21 serum levels correlated positively with insulin and HOMA index (rs=0,49 and rs=0.47) and correlated inversely with QUICKI index and SHBG (rs=–0.46 and rs=–0.51).
Conclusions
There was no stimulatory effect of thyroid hormones on FGF21 secretion. Circulating FGF21 rose markedly in rapidly developing hypothyroidism after radioiodine treatment and associated with the increase in triglycerides and cholesterol serum levels. In the critical metabolic state of lipid overload, FGF21 secretion may have a compensatory effect promoting lipid oxidation.

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AEP295

Excess risk of thyroid cancer in individuals with type 1 diabetes compared to those without diabetes in Finland; nationwide study

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The prevalence and possible excess risk of thyroid cancer in T1D compared to individuals without T1D is poorly known. Therefore, the aim of this study was to assess excess risk of thyroid cancer in adults with long-term T1D compared to sex- and age-matched control individuals.
Study included 4758 individuals with T1D from the Finnish Diabetic Nephropathy (FinnDiane) Study. For each individual, three nondiabetic control individuals who were matched for sex, age, and place of residence in the year of diagnosis of diabetes in the FinnDiane patient, were selected from the Finnish Public Registry, altogether 12710. The thyroid cancers were identified by linking the data with the Finnish Care Register for Health Care (data available for the years 1970–2015). The types of cancers as well as the presence of metastaseswere assessed by reviewing the medical records. Cochran–Mantel–Haenszel test was used to compare risks and produce odds ratios (ORs)with 95% confidence intervals (CI) between individuals with T1D and controls.
The median age of the FinnDiane individuals at the end of follow-up in 2015 or death was 51.4 (IQR 42.6–60.1) years. As many as 27 (0.57%) had thyroid cancer, compared to 27 (0.21%) in the control individuals giving rise to an OR of 2.67 (95% CI 1.57–4.56, P=0.0002). The median age at diagnosis of thyroid cancer was 38.5 years (IQR 33.6–46.6) in T1D and 42.8 years

(29.4–49.9) in controls ($P=0.83$). Women had higher risk in the controls (OR=3.07 (1.30–7.26) while the risk in T1D was no different between the sexes, OR=1.61 (0.74–3.47). Median HbA1c was 8.8% (8.2–9.5) in those with T1D and thyroid cancer while it was 8.3% (7.4–9.2) in the rest of the FinnDiane individuals ($P<0.0001$). 16.7% of thyroid cancers were associated with thyroid autoimmunity.
The distribution of different types of thyroid cancers was similar in those with T1D and the controls. Most of the cancers were papillary; 81.5% in T1D and 88.9% in the controls, while 14.8% were follicular in T1D and 11.1% in the controls. There was only one medullary cancer in T1D. Signs of metastases were observed in 2 out of 27 individuals with T1D and in 7 out of 27 in the controls ($P=0.12$).
The prevalence of thyroid cancer is 2.7 fold in individuals with T1D and equal between the sexes. The data suggest that poor glycemic control is associated with risk of thyroid cancer in T1D.

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AEP296

Pulse wave velocity and circulating Retinol binding protein 4: A cross sectional association in early postmenopausal women

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Introduction
Recent evidence recognized the value of Retinol-Binding Protein (RBP4), as potential biomarker of cardiovascular and cerebrovascular pathology. The possible association between RBP4 and functional vascular disease remains unexplored, while recent data in postmenopausal populations suggested lack of association between RBP4 and subclinical atherosclerosis. We evaluated the possible link between RBP4 and menopause-specific cardiovascular risk factors, in a sample of apparently healthy postmenopausal women.
Methods
We recruited 123 healthy postmenopausal women, retrieved from a University Menopause Clinic. Inclusion criteria were menopausal age of equal or less than 10 years. Exclusion criteria were: 1) no intake of hormone therapy, antihypertensive, Participating women were not on treatment with hormone therapy, antihypertensives or hypolipidemic treatment. Women were instructed to fast for at least 8 hours and not to smoke, aiming for a blood tests for biochemical/hormonal assessment. Sonographical evaluation was performed immediately thereafter and included carotid-femoral pulse wave velocity (PWV) and calculation of the carotid artery stiffness index (S.I.)
Results
Univariate correlations were observed between RBP4 values and age, LDL-cholesterol and marginally significant with S.I., PWV, homocysteine, circulating estrogen, triglycerides. Women with RBP4 values higher than the median vs lower RBP4 values presented with higher levels of homocysteine (homocysteine: RBP4<10.5 ng/ml vs≥10.5 ng/ml: 11.2±2.81 μmol/l vs 12.52±3.44 μmol/l, P-value=0.049 ANCOVA adjusted for age, BMI, HOMA-IR). PWV was independently associated with RBP4 (b-coefficient=0.440, P-value=0.007), in multivariate models adjusted for age, menopausal age, LDL-cholesterol, circulating estrogen, smoking, pulse pressure, homocysteine, Similarly, S.I. was associated with RBP4 levels (b-coefficient=0.324, P-value=0.039) and insulin resistance, in models adjusted forage, menopausal age, LDL-cholesterol, circulating estrogen, smoking.
Conclusions
The results of this study show that higher RBP4 serumlevels are associatedwith greater aortic and carotid stiffness, in a sample of healthy postmenopausal women. Larger studies are required to further elucidate the significance of our findings.

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AEP297

Metabolic syndrome severity score for predicting cardiovascular events: A nationwide population-based study from Korea

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Background and aims
Recently, a metabolic syndrome severity score (MS score) using a dataset of the Korea National Health and Nutrition Examination Surveys has been developed. We aimed to determine whether the newly developed score is a significant predictor of cardiovascular (CV) events among the Korean population.
Methods
From the Korean National Health Insurance System, 2,541,364 (aged 40–59 years) subjects with no history of CV events (ischemic stroke or myocardial infarction [MI]), who underwent health examinations from 2009–2011 and were followed up until 2014–2017, were identified. Cox proportional hazard model was employed to investigate the association between MS score and CV events. Model performance of MS score for predicting CV events was compared to that of conventional metabolic syndrome diagnostic criteria (ATP-III) using the Akaike information criterion and the area under the receiver operating characteristic curve.
Results
Over a median follow-up of 6 years, 15,762 cases of CV events were reported. MS score at baseline showed a linear association with incident CV events. In themultivariable-adjusted model, the hazard ratios (95% confidence intervals) comparing the highest vs lowest quartiles of MS score were 1.48 (1.36–1.60) for MI and 1.89 (1.74–2.05) forstroke. Model fitness and performance of the MS score in predicting CV events were superior to those of ATP-III (Table 1).

Table 1 Model fit analysis and model performance of metabolic syndrome indicators.

Event	Model	MS indicator	AIC	AUC (95% CI)	*P*-value*
CV events					
	1	ATP-III	181,473.2	0.718 (0.714–0.722)	<0.001
		MS score	181,292.2	0.720 (0.716–0.724)	
	2	ATP-III	183,029.2	0.704 (0.700–0.708)	<0.001
		MS score	182,600.6	0.708 (0.704–0.712)	
Stroke					
	1	ATP-III	100,892.9	0.705 (0.699–0.711)	0.003
		MS score	100,828.8	0.707 (0.701–0.712)	
	3	ATP-III	101,508.2	0.693 (0.688–0.699)	0.003
		MS score	101,406.9	0.696 (0.690–0.702)	
MI					
	1	ATP-III	103,820.7	0.741 (0.735–0.746)	<0.001
		MS score	103,696.9	0.743 (0.738–0.748)	
	3	ATP-III	105,174.2	0.720 (0.714–0.725)	<0.001
		MS score	104,813.0	0.726 (0.721–0.731)	

Model 1: adjusted for age, body mass index, current smoking, heavy alcohol consumption, regular exercise, and family income
Model 2: Model 1+ further adjusted presence of hypertension, diabetes, medication for dyslipidemia, and total cholesterol.
**P*-value: DeLong's test for ROC curves of two metabolic syndrome indicators.

Conclusions
The newly developed age- and sex-specific continuous MS score for the Korean population is an independent predictor of ischemic stroke and MI in Korean middle-aged adults even after adjusting for confounding factors.

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AEP298

High prevalence of cognitive dysfunction and vitamin B12 deficiency in patients with type 2 diabetes over 50 years

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Introduction
Hyperglycemia is a common disorder in elderly patients. Diabetes management in this population requires evaluation of medical, pharmacological and functional domains. Screening for diabetes chronic complications should include, in addition to traditional micro- and macrovascular disease, search for cognitive impairment and vitamin B12 deficiency.
Objective
To evaluate the prevalence of cognitive impairment, depression, and associated clinical variables in a population of adult patients with type 2 diabetes.
Methods
Individuals over 50 years and with type 2 diabetes, assisted at the Federal University of Pelotas, South of Brazil, were included in the study. We performed a cross-sectional study with application of a face-to-face questionnaire and evaluation of outpatient clinical records for clinical and demographic variables analysis. We use Mini-Mental State Examination (MMSE) to assess cognitive impairment, and Patient Health Questionnaire-2 (PHQ) and PHQ-9 to evaluate depression.
Results
We included 116 patients, with a median age of 62 years, 68.1% were women, 76.7% have white skin color, and 81% have 8 years of study or less. The mean A1c was 9.6%. Over 70% of the patients have at least one microvascular complication, and 52.6% have clinical macrovascular disease. The prevalence of cognitive dysfunction was 35.3% and that of depression was 33.6%. The group of patients with cognitive dysfunction has higher rates of B12 deficiency (60% vs 36.6% in controls; $P=0.01$) and of benzodiazepine use (51.3% vs 30.6% in controls; $P=0.03$). The presence of microvascular complications was also higher in the group of patients with cognitive dysfunction (85.4% vs 66.7% in controls, $P=0.003$). Other clinical variables were not different between groups. B12 deficiency was associated with cognitive impairment even after adjustments [1.78 (1.07–2.98)]; while the association with benzodiazepine use was not significant after statistical adjustments [1.58 (0.95–2.64)].
Discussion
Patients over 50 years and with type 2 diabetes have a high prevalence of cognitive dysfunction and depression, and B12 deficiency was associated with cognitive impairment. Therefore, we strongly suggest that clinical doctors actively search for these comorbidities.

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AEP299

Prevalance of undiagnosed dementia in young diabetic population in central india

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Dementia is increasing day by day as longevity is increasing. There is a underlying need to evaluate Dementiaamongst Diabetics as they are more prone for dementia, By identifying early and preventing the incidence or advance of microangiopathy we can play an important role in maintaining quality of life and reducing mortality in patients with diabetes mellitus. Type 2 diabetes is a robust cause of cognitive impairment and decline in even in younger adults.
Multiple population-based studies have reported an association between Type 2 diabetes and cognitive impairment and older adults with Type 2 diabetes experience global cognitive decline at a rate that is double those without Type 2 diabetes over a 5-year period. General cognitive slowing, thought to be a marker for accelerated brain aging and dementia risk, is related to Type 2 diabetes in middle-aged and older adults.
Patient were selected from central india and inclusion criteria were: diagnosis of Type 2 diabetes; age between 20–60 years; no peripheral or central vestibulopathy or any other neurological disease, no history ofcerebrovascular accident and myocardial infarction. 324 diabetics and 306 non diabeticwere randomly selected, screened by using mini mental status examination questionnaire in local language, results were analysed
A prevalance of 6.7 percent was seen in young diabetics, more in females, non smart phone users, and having low academic qualification, As compared to Non- Diabetics who had a prevalance of 0.7 percent.
There is no data regarding prevalance of dementiain young diabetics in india.
The current understanding about dementia is inadequate for development of appropriate feasible tools for screening the population in early phase of dementia as there is a dearth of manpower and financial resources and huge gaps in research, especially in areas of pathophysiology and disease-modifying pharmacological agents. Therefore, the only viable option as of now is primary prevention of dementia by addressing risk factors and promotion of protective factors. However, for effective handling of epidemic, we need to empower the health-care workers and professionals in screening and management of dementia. An effective systemic health-care model should be developed for delivery of services to the families and patients with dementia keeping our sociocultural beliefs in mind. Every step should be taken to improve awareness regarding dementia and its preventive measures, to halt the epidemic, thereby contributing to a healthy and prosperous nation.

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AEP300

Features of phenotypes of diabetic kidney disease depending on the type of underlying disease

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Introduction
Chronic kidney disease (CKD) is one of the leading causes ofdisability and mortality in patients with diabetes mellitus. Existence of specific phenotypes of diabetic kidney disease (DKD) is established nowadays. The prevalence of the classic albuminuric phenotype has decreased by 24% over the past decade (NHANES).
The purpose of our work was to investigate the phenotypic features of DKD depending on the type of diabetes.
Materials and methods
A comprehensive survey of 1576 patients with diabetes was analyzed, 447 of which were of type 1 diabetes mellitus (T1DM), 1041 were of type 2 diabetes mellitus (T2DM) and 88 patients were with latent autoimmune diabetes in adult (LADA). We studied the frequency and features of the course of CKD, as well as the prevalence of phenotypic forms of DKD: classical albuminuria, nonalbuminuric renal dysfunction and progressive decrease in renal function. Glomerular filtration rate (GFR) was evaluated using the CKD-ERI formula, albuminuria, albumin-creatinine ratio (AKR), and kidney ultrasound were analyzed.
Results
The incidence of CKD in T1DM was 38% (203 patients), 23% (242 patients) in T2DM and 30% (34 patients) in LADA. In T1DM, CKD stage was recorded with the following frequency: G1 – 24%, G2 – 58%, G3a – 16%, G3b – 1%; by albuminuria category: A1 – 21%, A2 – 79%. In T2DM, stage G1 occurred in 8% of patients, G2 in 48%, G3a in 26%, Gb in 14%, G4 in 4% of patients; albuminuria in stage A1 was reported in 29% of patients, and A2 in 71%. In turn, with LADA G1 stage CKD occurred in 17% of patients, G2 – in 63%, G3a – in 16%, G3b – in 3%, G 4 – in 1%; albuminuria in stage A1 was reported in 37% of patients, and A2 in 63%. Classical albuminuric phenotype was reported in 21% of patients with T1DM, 29% of patients with T2DM, and 25% of patients with LADA. The proportion of patients with nonalbuminuric renal dysfunction was 60% for T1DM, 43% for T2DM, and 53% for LADA. In turn, progressive kidney damage was detected in 19% of T1DM, 28% of T2DM, and 22% of LADA cases.
Conclusion
Nonalbuminuric DKD was observed in 60% of cases of T1DM, in T2DM – 43%, while LADA was diagnosed in 53% of cases. The incidence of classic albuminuric phenotype is higher in T2DM, and progressive kidney damage is 1.5 times higher than in patients with T1DM and LADA.

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AEP301

Maturity- onset diabetes of the young type 6 (MODY6): A case report of two relatives (mother and daughter) with undescribed heterozygous variant of mutation in NeuroD1 gene

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A 37-year-old Caucasian female, pharmacist, referred to Diabetological center in February 2017. The main complaint was frequent urination.
Medical history
She was diagnosed with T2DM at the age of 32 year. She was taking Metformin 850 mg twice daily. Her plasma glucose was 7.8 mmol/l at fasting; 10.8 mmol/l postprandial.
Family history
Her father has elevated glucose levels also (up to 8 mmol/l before meal). Her mother has passed away soon after the delivery of her second child at the age of 31 year (baby died also on the second day after birth).
Patient has a 12- year- old daughter.
Physical examination
BMI is 23 kg/m^2 (height 157 cm, weight 56 kg)
No other NeuroD1-associated clinical phenotypes, including cerebellum hypoplasia, psychic development retardation, sensorineural bradyacuasia or visual impairment were revealed.
Laboratory findings
Her HbA1c was 5.77%, C-peptide level was 1.52 ng/ml (1.07–11.8 ng/ml); glutamate decarboxylase and pancreatic islet antibodies were negative.
The probability of patient having MODY was 58% (using Diabetes Diagnostics calculator by Exeter University).
Patient`s daughter glycemia was 9.8 mmol/l at random site. She had not been diagnosed with diabetes mellitus previously. Her HbA1c was 6.3%, C-peptide level was 1.96 ng\ml (1.07–11.8 ng/ml); glutamate decarboxylase, zinc transporter 8 and IA-8 antibodies were negative. The results of the oral glucose tolerance test were 6.4 mmol/l at fasting, 12.3 mmol/l after 30 minutes, 15.3 mmol/l after 60 minutes, 13.6 mmol/l after 120 minutes.
In July 2017 the mutation in the neurogenic differentiation factor 1 gene (NeuroD1) was revealed in both patients (a heterozygous undescribed previously mutation variant c. 1022A>T: p. H341L. The analysis was performed at The National Endocrinology Research Centre. Moscow) The diagnosis of MODY6 was established.
To the date both patients take no medication. Their blood glucose levels are 6–7 mmol/l at fasting, 6–8 mmol/l after the meal.

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AEP302

Challengesrelated to prevention and management of diabetes mellitus inprimary healthcare settings

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Introduction
Over 94% of total mortality in Georgia is attributable to non-communicable diseases (NCDs). Alhought various NCDs guidelines and protocols have been developed and approved in Georgia, their implementation at the primary healthcare (PHC) level has not been successful. The AIM of the study was to assess PHCs approaches to prevention and management of diabetes.
Methods
General practitioners (GPs), family and village doctors were involved in a cross-sectional survey with two-stage random sampling design, that was conducted in two regions of Georgia: Stage 1 – sampling frame consisted of all PHCs/village ambulances of the selected regions; Stage 2 – randomly selected family and village doctors from each of the selected facility. Study tool: Self-Completed Questionnairebased on the Package of Essential NCDs (PEN) interventions for PHC. Mean score for knowledge for diabetes (DM) management and control was calculated and compared among professional groups (family vs village doctors) and regions (Tbilisi vs Kakheti) using one-way Analysis of Variance.
Results
In total, 293 doctors (mean age 54.3±12.0 years) participated in the study. Participants were more experienced in management and control of DM than other NCDs. About two thirds of respondents had good knowledge on management and control of DM, they managed to response correctly to 80% of questions. Mean score for knowledge of DM management and control was almost similar among family and village doctors (*P=0.31)*, as well asbetween the regions (*P=0.01*). Although over 80% of physicians have positive attitudes towards prevention and management of DM, smoking was the only status of patients' that was 'always' determined bydoctors (80% of doctors; 95%CI=72.6%–82.4%); less than 50% (95%CI=40.2%–51.7%) of doctors collected information about body mass index (BMI); approximately 50% (95%CI=41.6%–53.3%) of them spent no more than 20 min in a typical visit of a patient with high glucose and⁄or high cholesterol levels.
Conclusions
Family/village doctors': 1. knowledge on DM and its risk factors is moderate, 2. management practices are relevant but not standardized, 3. attitudes towards DM screening andprevention are positive. These findings highlight the needs of effective interventions among family/village doctors to ensure that they are actively involved in prevention and management of DM.

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AEP303

An assessment into the insulin secretion during visceral leishmaniasis

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Objective
Visceral Leishmaniasis is a macrophage associated disorder. About 5 percent of the patients may develop insulin dependent diabetes mellitus. It appears to have a direct action on pancreatic beta cells, resulting in initial insulin release followed by impaired insulin secretion. Within this context we looked into alternate therapies of treatment.
Methods
In this study, we investigated whether alteration in the CD2 mediated coordination of an immune response was associated with down regulation of CD4 associated Th1 cell response during Visceral Leishmaniasis (VL) and insulin secretion.
Results
Leishmania donovani (Ld) infection in VL patients markedly reduced expression of CD2 cell surface antigen on CD4+ cells. T-cells of VL patients were mostly in G0/G1 stage of the cell cycle (98.20%) with little or no activity of protein kinase C-alpha (PKC-alpha) isoform. However, pre-incubation with activating anti-CD2 monoclonal antibody (MAb) resulted in a corresponding increase up to 2.52-fold in T-cells of G2/M population supported by both activity and expression of PKC-alpha isoform.
Conclusion
These findings imply that infection with L. donovani induces less CD2 on the surface of CD4+ T-cells, which once activated orchestrate the protective IFN-gamma dominant host defense mechanism via PKC-mediated signal transduction and cell cycle but sugar control strategies must also be undertaken simultaneously to circumvent infection.

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AEP304

Diagnostic accuracy of fatty liver index in type 1 diabetes mellitus patients

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Introduction
Nonalcoholic fatty liver disease (NAFLD) affects ±55% of subjects with type 2 diabetes and contributes to cardiovascular mortality. NAFLD data in type 1 diabetes (T1DM) are scarce. Biopsy is the diagnostic reference but is not suited for routine screening. Ultrasound (US) is validated to diagnose steatosis as first-line imaging but is restricted to trained operators. The Fatty Liver Index (FLI) is a score to predict fatty liver based on triglycerides, Body Mass Index (BMI), gamma-glutamyl-transpeptidase (GGT) and waist circumference (WC), and stratifies risk groups in primary work-up. FLI <30 is considered to rule out steatosis, FLI ≥60 to rule in steatosis and trigger

referral. We investigated the reliability of FLI to predict steatosis using ultrasound as the reference method in T1DM.
Methods
We consecutively recruited 331 T1DM patients who underwent anthropometry, US and lab-tests. We used the area under the receiver operating characteristic curve (AUROC) and Youden's Index to determine diagnostic accuracy.
Results
Prevalence of steatosis was 22% (74/331) based on US. WC (89±13 vs 103±14 cm, $P \leq 0.001$), BMI (25. 3±4.1 vs 30.0±4.9 kg/m^2, $P \leq 0.001$), GGT (33±2 vs 47±5 mU/l, $P=0.007$), HDL (64±16 vs 58±18 mg/dl, $P=0.005$) and triglycerides (80±40 vs 113±84 mg/dl, $P \leq 0.001$) differed significantly between the steatosis and non-steatosis group. Age, gender and ALT did not differ. The AUROC of the FLI for diagnosis of steatosis was 0.78 (95% CI: 0.71–0.84). Optimal cut-off according to Youden's Index was ≥30 (sensitivity 0.84, specificity 0.63, PPV 0.82, NPV 0.92). Thirteen subjects with steatosis on US had a FLI <30 (13/175:7.4%). We further assessed the predefined threshold of ≥60 (sensitivity 0.55, specificity 0.84, PPV 0.50 and NPV 0.87). Thirty-three out of 74 patients with steatosis had a FLI <60, so 45% of cases would not be diagnosed. Comparison of groups with FLI <30 and FLI 30–59 showed significant differences in systolic blood pressure (133±17 vs 140±20 mmHg, $P=0.004$), creatinine (0.8±0.2 vs 0.9±0.6 mg/dl, $P=0.007$) and HDL (67±17 vs 57±16 mg/dl, $P<0.001$), indicating a higher metabolic risk profile in the latter.
Conclusion
Diagnostic accuracy of FLI for diagnosis of steatosis is moderate in T1DM patients with optimal cutoff ≥30. The FLI cutoff ≥60 would miss the diagnosis of steatosis in 45% of cases, whereas the cutoff ≥30 would miss only 7.4%. The subjects with a FLI score 30–59 had a more severe risk profile compared to subjects with FLI <30. Therefore, we propose the cutoff ≥30 in primary decision making based on FLI to diagnose NAFLD in T1DM patients.

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AEP305

CTRP-1 levels are related to insulin resistance in gestational diabetes mellitus

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Introduction
CTRP-1 belongs to the adipose tissue-derived C1qTNF superfamily of proteins involved in e.g. glucose metabolism regulation. Recent studies have shown significant differences in CTRP-1 levels between type 2 diabetics and controls. We aim at investigating a possible link between gestational diabetes mellitus (GDM) and CTRP-1 as there is little data on CTRP-1 and its possible functions in pregnancy.
Patients and Methods
In 167 women (93 with normal glucose tolerance (NGT), 74 GDM) of a high-risk population for GDM at a tertiary treatment center, CTRP-1 levels were investigated in respect to GDM. Glucose tolerance, insulin resistance and secretion were assessed with indices (Matsuda index, Stumvoll first phase index, ISSI- 2, AUC insulin, AUC glucose) derived from an oral glucose tolerance test (oGTT) performed at <21 weeks of gestation (GW) and GW 24 to 28. GDM (44.3% of whole cohort) was further divided into GDM subtypes depending on a predominant insulin sensitivity (GDM-IR) or secretion deficit (GDM-IS).
Results
There was no significant difference in CTRP-1 levels between GDM (mea $n=76.86$ ng/ml; S.D.=37.81) compared to NGT ($P=0.104$). However, GDM-IR women (44.00±43.00 ng/ml) had significantly lower CTRP-1 levels compared to the GDM-IS group (83.79±23.08 ng/ml; $P<0.001$) and women with NGT (82.2±35.34 ng/ml; $P<0.001$) Throughout pregnancy, CTRP-1 levels did not change significantly, except for the GDM-IR group. Here, CTRP-1displayed a downwards trend when correlated with gestation week. In the whole population, CTRP-1 levels correlated negatively with BMI, diastolic blood pressure, AUC insulin, adiponectin levels, fetal birth weight and positively with HbA1c, Matsuda Index and ISSI-2.
Conclusion
The results of the present study further point towards CTRP-1 being a metabolic biomarker for insulin resistance in GDM. To establish its exact function, further investigations on CTRP-1 in relation to hyperglycemia and insulin resistance are imperative.

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AEP306

New-onset diabetes mellitus after liver transplantation in the patients with acute liver failure: Is there any effect of pretransplant hypoglycemia?

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Introduction
The frequency of new-onset diabetes after transplant (NODAT) is 5–30% in liver transplant recipients. We aimed to analyze the frequency and predictors of NODAT in the patients undergoing liver transplantation (LTx) due to acute liver failure(ALF), and to investigate whether pretransplant hypoglycemia had any effect on NODAT.
Materials and methods
Adult patients undergoing LTx due to ALF were analyzed retrospectively. The patients with chronic liver failure or diabetes were excluded. We measured pretransplant random blood glucose(RBG) and posttransplant fasting blood glucose(FBG). NODAT was diagnosed according to principally 1st month FBG (group 1:<100, group 2:100–125, group 3:>125 mg/dl). The participants were subgrouped according to age, gender, BM, etiology, antiviral medication, thyroid function, pretransplant RBG, donor type, immunosuppressive drug, common infection, and surgical complication.
Results
A total of 91 patients were analyzed; mean age was 33.48 (±13.35), and 52.7% ($n=48$) of them was female. The etiology was Budd-Chiari syndrome in 3 (3.29%), acute viral hepatitis in 38 (41.75%), drug or toxin-related in 21 (23.07%), and other/unknown causes in 29 (31.86%) patients. The ratio of NODAT was 26.98% on the 1st month. NODAT group had a higher pretransplant RBG than the others. Pretransplant hypoglycemia did not have any effect on NODAT; however, pretransplant hyperglycemia increased the risk of NODAT by 4.065 times ($P=0.018$).
Conclusions
We showed that pretransplant hyperglycemia increased the risk of NODAT by 4 times, but hypoglycemia did not affect. The frequency of NODAT decreased progressively during follow-up. We recommend perioperative glycemic control should be maintained as early as possible to manage NODAT; however, it might be complicated in such a clinical condition.

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AEP307

Perception regarding marriage of diabetics in central indian population

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Background
Marriage is an integral part of Indian society. In spite of the large number of people with diabetes mellitus (DM) in India, India is not a diabetes-friendly society. The society suffers from lots of myths regarding diabetes and insulin use. This survey highlights perceptions of general population with regards to marriage, associated diabetes distress, and suggests potential solutions. If no one is ready to accept diabetics as a bride or groom for their children and they can't have a family, it's a serious issue. There is no survey till date on this topic with surveyed population.
Methods
1365 Randomly selected people, males and females, from rural and urban areas of central India were asked to fill a survey questionnaire online as well as in paper. The inclusion criteria were age 30–60, having at least one children and no history of mental disorder. The results were analyzed, inclusion criteria were age 30–60, no history of mental disorder.
Results
Responses were analyzed and plotted. Most of the respondents (78%) were not willing to accept a diabetic groom or bride for their children, the acceptability was more in males, persons coming from urban areas, having higher academic qualification, and in those with children with diabetes, the acceptability in even the known diabetics is only 15%. Most of the responders were worried about the complication of the disease. Majority of responders (74%) think diabetes affect future progeny.

Conclusion
Misconception regarding social, occupational, marital abilities, fertility, genetics, quality of life in young people living with DM raises major barriers to marriage, People with DM are wrongly assumed to be sick, disabled, dependent persons, unsuitable for marriages, and likely to have complicated pregnancies with the possibility of having children with diabetes. Diabetes distress and psychological issues are major problems related to marriage in young people with DM. Counseling of patients, family, relatives, prospective spouse, and increasing social awareness regarding diabetes through mass communication will serve as the keys to their resolution.

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AEP308

Effect of maternal obesity and degree of glucose intolerance on neonatal hypoglycaemia and birth weight: A retrospective observational cohort study in women with gestational diabetes mellitus

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Introduction
Gestational diabetes mellitus (GDM) is an increasing problem worldwide. Post-natal-hypoglycaemia and excess-foetal-growth are known important metabolic complications of neonates born to women with diabetes. This retrospective-cohort-study aims to determine the influence of obesity and glucose-intolerance on neonatal-hypoglycaemia and birth-weight over the 90th percentile (LGA).
Methods
Data were abstracted from 303 patient medical records from singleton pregnancies diagnosed with GDM. Data were recorded during routine hospital visits. Demographic data were acquired by facilitated questionnaires and anthropometrics measured at the first antenatal appointment. Blood-biochemical-indices were recorded. Plasma glucose area under the curve (PG-AUC) was calculated from 75 g oral glucose tolerance (OGTT) results as an index of glucose intolerance.
Results
OGTT results of 303 pregnant women aged between 33.6 y (29.8–37.7), diagnosed with GDM were described. Neonates of mothers with a BMI of over 30 $kg.m^{-2}$ were more likely to experience neonatal hypoglycaemia (24 (9.2%) vs 23 (8.8%), $P=0.016$) with odds-ratio for neonatal-hypoglycaemia significantly higher at 2.105, 95% CI (1.108,4.00), $P=0.023$. ROC analysis showed poor strength of association (AUC 0.587 (95% CI, .487 to .687). Neonatal LGA was neither associated with nor predicted PG-AUC or obesity; however, multiparous women were 2.8 (95% CI (1.14, 6.78), $P=0.024$) times more likely to have a baby born LGA.

Table 1 Maternal and neonatal characteristics stratified according to maternal BMI at 12 weeks gestation.

	BMI < 30 $kg.m^{-2}$	BMI ≥ 30 $kg.m^{-2}$	*P*-value
n	188	107	–
Maternal age (y)	33.1 (29.6–36.8)	34.8 (26.1–38.3)	0.141
Previous GDM	32 (10.9%)	34 (11.6%)	0.003**
Fasting plasma glucose (mmol/l)	4.6 (4.3–5.2)	5.1 (4.5-5.3)	<0.001***
1 h post 75 g glucose challenge (mmol/l)	10.2 (9.1–10.7)	(8.9–10.9)	0.885
2 h post 75 g glucose challenge (mmol/l)	7.0 (6.2–8.4)	6.6 (5.9–8.3)	0.315
PGAUC	25 (23.0–26.0)	24 (22.0–27.0)	0.745
Required insulin treatment	16 (5.4%)	19 (6.4%)	0.018*
Macrosomia	18 (6.1%)	17(5.8%)	0.107
LGA	23 (7.9%)	16 (5.5%)	0.542
NNU admission	33 (11.2%)	27 (9.2%)	0.116
Age adjusted birth centile	53.9 (31.1–77.1)	39.9 (16.4–79.6)	0.052
Neonatal hypoglycaemia	23 (8.8%)	24 (9.2%)	0.016*

Conclusion
Maternal BMI during the first trimester of pregnancy exhibits a strong influence on neonatal hypoglycaemia but not neonatal birthweight in a cohort of pregnancies affected by GDM. Multiparous women are more likely to have an infant born LGA. Future studies should examine the relationship between maternal adiposity, together with accurate markers of insulin sensitivityon the outcome of neonatal hypoglycaemia.
Data presented as median (IQR) or where frequency Count (percentage).
*denotes significant difference ($P<0.05$),
**denotes significance $P<0.01$, ***denotes significance $P<0.001$.

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AEP309

Untargeted plasma metabolomics identifies broad metabolic perturbations in glycogen storage disease type I

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Background/Introduction
The primary metabolic defect in glycogen storage disease type I (GSDI) results in fasting hypoglycemia and typical secondary metabolic abnormalities (e.g. hypertriglyceridemia, hyperlactatemia, hyperuricemia). The aim of this study was to broadly assess further perturbations of the metabolic network in GSDI by using untargeted plasma metabolomics.
Methods
Plasma samples of 14 adult GSDI patients (11 GSDIa, 3 GSDIb. Mean age 26.4 y, range 16–46 y) on standard treatment were compared to a cohort of 31 healthy controls utilizing ultra-high performance liquid chromatography (UHPLC) in combination with high resolution tandem mass spectrometry (HR-MS/MS) and subsequent statistical multivariate analysis. Significantly altered features were identified by mining against an internal library as well as online databases Metlin and mzCloud.
Results
The metabolic profile showed numerous alterations of metabolites in different areas of the metabolic network, e.g. in central pathways of energy generation such as the tricarboxylic acid cycle, in the metabolism of creatine, in the urea cycle, in the amino acid and purine/pyrimidine metabolism, but also changes of enzyme cofactors such as biotin. These metabolic alterations were consistently seen in patients of both GSD subtypes (Ia and Ib).
Conclusion
The metabolic defect of GSDI has profound effects on a variety of metabolic pathways in both GSDI subtypes, in addition to the known typical metabolic abnormalities (e.g. in lipid metabolism). The effect of glycemic control on these metabolic alterations, as well as the mechanisms behind these observations remain to be further elucidated.

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AEP310

Characterization of muscle function, lifestyle and motivational indices in obese women

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Introduction
Obesity is a chronic metabolic condition characterized by an excess of adipose tissue leading to an increased risk of developingdiseases such as diabetes mellitus and cardiovascular pathologies. Unbalanced nutrition and sedentary lifestyle are among the main influencing factors leading to a reduction in muscle mass, strength and functionality, predisposing obese subjects to sarcopenia and functional disability. Moreover, recent studies suggest the possible presence, in these patients, of alterations in their volition in performing lifestyle actions. Thus, the aim of our study was to evaluate the possible correlations among indices of muscular function (MF), lifestyle and volition.
Methods
Twenty-one obese women (age: 41.8±11.8 years; BMI: 38.2±3.2 kg/m^2) were recruited at the High Specialization Center for Obesity Care, Policlinico Umberto I, Sapienza University of Rome. After clinical assessment, all subjects were evaluated for: Body composition (BC) by DXA, and for upper and lower limbs indices of MF by Handgrip test (HGT) and Sit to Stand 30s (STS). Furthermore GPAQ, Predimed questionnaire to determine the Mediterranean diet (MeDi)adherence, Volition Exercise Questionnaire (VEQ), Exercise Motivations Inventory (EMI-2), Psychobiosocial States in Physical Education (PBS-SPE), Decisional Balance Inventory (DBI) and physical activity level (PAL) motivational indices were administered, in order to evaluate individual lifestyle. Potential relationships among all variables were analyzed by Pearson correlation.
Results
BCshowed high percentage Fat Mass (40.9±3.4%) and low level of Lean Mass (59,1±4,5%). The results of the T-tests with independent samples showed no significant differences between sedentary and active groups, for questionnaire and motor test variables. Furthermore, correlations indicate a significant relationship between the HGT strength indices and the GPAQ, but not with STS. Finally, the facilitatory volition correlates positively with the STS, while the inhibitory one correlates negatively (R=0.52; R=–0.39; P<0.05).
Conclusions
In conclusion, our results indicate that high PAL and good adherence to MeDi do not correlate with the STS, which show indices below normal level. However, it is interesting how STS positively correlates with VEQ. Literature data suggestHGT as the most suitable tool for assessing general muscle strength, but results suggest greater relevance of STS as an indicator of poor MF while also detecting a discrepancy between upper and lower limb MF. Therefore, an interdisciplinary holistic evaluation is essential in obese subjects to define and validate the parameters indicative of health status and muscle functionality.

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AEP311

Study of the effect of sibutramine on central mechanisms of regulation of eating behavior in patients with obesity by means of fMRI. Preliminary results

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Introduction
Patient's nutrition is generally considered to be the main cause of the accumulation of excess body weight. However, this accumulation can be mitigated by treatment involving drugs with a central mechanism of action. By using functional Magnetic Resonance Imaging (fMRI) we can meliorate our understanding of the organization of neuronal networks responsible for eating behavior, and see how they respond to the mechanisms of action of sibutramine in the treatment of the obesity.
Purpose
To assess changes in eating behavior by fMRI in obesity patients, who took sibutramine for 3 months.
Methods
The study included 30 patients (87% women) with obesity having BMI of ≥30 kg/m^2 with mean age of 32.6 years, mean body weight (BW) – 110.0 kg, mean waist circumference – 109.8 cm. All patients were right-handed. The control group included 23 people with normal BMI of comparable gender and age. All participants underwent initial fMRI-mapping focused on the dominant hemisphere of the brain. The obesity cohort was treated with sibutramine (Reduxine) at a dose of 10 or 15 mg per day for 3 months. After treatment patients with obesity underwent a second fMRI mapping to assess changes against the initial mapping.
Results
According to fMRI in the group with obesity (before treatment), there was a lower activation of the upper and lower parietal lobes in both hemispheres as well as a lower activation the lateral right frontal cortex compared to the healthy control group. Furthermore, in the obese group there was also a pronounced activation in regions 45, 46, and 9 in the DorsoLateral PreFrontal Cortex (DLPFC) of Broadman fields on the left. Activation of the Supplemental Motor Area (SMA) and DLPFC on the right in patients with obesity was absent, compared to the control group. After 3 months of treatment with sibutramine 80% of patients lose ≥5% of BW. After treatment in obese individuals there was a decrease in activation of the visual cortex, DLPFC and the appearance of activation in area 8 of the Broadman field on the left.
Conclusion
DLPFC and SMA are essential parts of the control neural network related to eating behavior. According to fMRI observations in this study, obese patients treated with sibutramine for 3 months, had a decrease in activation in the projection of the left DLPFC what was regarded as a change in disordered patterns of eating and may indicate increased appetite control due to the treatment.

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AEP312

Combination of baseline body weight with active plasma ghrelin level could predict early response with liraglutide 3.0 mg in patients with obesity

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Introduction
Liraglutide 3.0 mg could be effective option for obesity management. It is known that patients who have ≥5% weight loss in 16 weeks ('early responders' (ERs)) will have ≥10% weight loss in 56 weeks [1]. Predictors of this early response (ER) in 16 weeks are unknown.
Methods
22 obese patients (30% men; median age 40.0 [33.0; 48.5]) were recruited. The exclusion criteria were diabetes, psychotic disorders, obesity due to secondary causes, deconditioning of concomitant diseases and current or 3-month prior usage of anti-obesity medications. Contraindications for liraglutide were excluded in all participants. Baseline body weight (BBW), BMI, waist circumference (WC) and eating behavior regulator levels in fasting state such as leptin, ghrelin, obestatin and GLP-1 (ELISA) were evaluated. Patients were prescribed liraglutide with standard dose escalation from 0.6 to 3.0 mg per day. In 16 weeks re-examination was performed. Statistical analysis include Wilcoxon and Mann-Whitney tests and linear regression analysis.
Results
Baseline plasma level for active ghrelin was 6.07 [3.41; 9.22] fmol/ml, for obestatin 1.85 [1.73; 2.26] ng/ml, for GLP-1 3.98 [2.91; 4.89] ng/ml and for leptin 66.49 [29.83; 108.12] ng/ml. The median (Me) of BBWchange was –7.30 [–11.50; –4.50] kg, Me BMI change –2.51 [–4.05; –1.39], Me WC change –6.00 [–9.50; –4.00]. All changes were statistically significant (P<0.007, Wilcoxon test). 14 patients (64%) lose ≥5% and 8 patients did not have ER. To identify predictor(s) of ER, baseline characteristics of ERs and non-ERs were compared. There was statistical tendency for smaller BBW in ERs (P=0.019, Mann-Whitney test). Since the study had limited number of observations, multivariate analysis was not used. With the method of linear regression analysis AUC for combinations of BBW with base-

line plasma eating behavior regulating-peptides were evaluated. The best AUC was for combination of BBW with active ghrelin level (0.893, 95% CI [0.708–0.989]). The mathematical model for result prediction was created. The quality of model due to the Hosmer-Lemeshov criteria was good (3.987; $P=0.858$). The sensitivity of model was 86%, 95% CI [65%; 97%], specificity 63%, 95% CI [41%;83%], predictive value of positive result 80%, 95% CI [60%; 95%], predictive value of negative result 71%, 95% CI [49%; 89%].
Conclusion
In our study, mathematical model including BBWin combination with plasma fasting active ghrelin level was a good tool for predicting probability of the effectiveness of liraglutide 3.0 mg therapy in patients with obesity with the sensitivity 86%. However, further studies with a larger sample of patients are required.

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AEP313

Omega-3 PUFA and probiotics as a single formulation for insulin resistance and obesity: Evidence from animals to randomized clinical studies

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Background
Probiotics and omega-3 polyunsaturated fatty acids supplementation (PUFA) have beneficial effect on obesity related disorders in animal models. We have previously shown, on rats with monosodium glutamate-induced obesity, that in take of the combination based on live probiotics and omega-3 PUFA is accompanied by the preventive effect concerning experimental obesity development, lead toinsulin resistance (IR) improvement and more obvious decrease of he paticsteatosis as well as lipid accumulation as compared to probiotic alone. Despite of animal data, randomized placebo-controlled trials (RCT) are still lacking or inconsistent.
In respect to our experimental data, we aimed to carry out place bo-controlled RCT for the efficiency of acombination of multi probiotics with omega-3 PUFA as anadjunction to the standardanti-diabetictherapy on the main metabolic parameters in T2D patients.
Methods
A total of 54 patients met the criteria and were included in double-blind single center RCT, to receive 'Symbiter-Omega' (biomass of 14 probiotic bacteria genera *Bifidobacterium, Lactobacillus, Lactococcus, Propionibacterium* withomega-3 PUFA as single formulation) or placebo for 8-weeks administered as a sachet formulation. The primary main outcome was the change HOMA2-IR (homeostasis model assessment-estimated insulin resistance). This model canbe calculated using the software available at http://www.dtu.ox.ac.uk/homacalculator/index.php. Secondary outcomes were the changes in glycemic control-related parameters, β-cells functionalactivity, anthropomorphic variables and markers of a chronic systemic inflammatory response.
Results
Combineduse of the probiotic mixture with omega-3 PUFA leadstoa significant reduction of HOMA2-IR ($P=0.018$) and improvement of insulin sensitivity (% S) ($P=0.010$) after 8 weeks of treatment period. Simultaneously were detected lowering of HbA1c from 8.26±0.82 to 7.80±0.86% ($P=0.006$). In patients that received placebo insignificant difference for both primary outcomes was found. Additionally, assecondaryoutcomesthefunctionalactivityofβ-cells (% B) was assessed. The intragroup analysis showed a trend to reduce the % B, which was more expressed in the placebo group. In secondary outcome analysis slight significant decrease of bodyweight and BMI as compared to placebo were found. Treatment with omega-3-enrichedprobiotics was accompanied by significant reduction of pro-inflammatorycytokines within intragroupcomparis on during the treatment, namely IL-1β ($P=0.015$), TNF-α ($P=0.002$), IL-6 ($P=0.001$) and IL-8 ($P=0.033$) correspondingly.
Conclusion
Probiotic combination with omega-3 PUFA modestly improved insulin resistance and obesity related parameters in patients with type 2 diabetes.

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AEP314

Antibodies to insulin receptor in the diagnosis of non-diabetic hypoglycemia

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Introduction
One of the autoimmunenon-diabetic hypoglycemia (NDH) causes isthe antibodies to insulinreceptor (AB-rIRI) formation and/orinsulin resistance type B (TBIR).
Objectives
To determine the prevalence of increased AB-rIRI level in patients with suspected NDH of different genesis and in healthy individuals; to determine significance of AB-rIRI investigation in NDH diagnosis.
Methods
In a prospective study we determined AB-rIRI (reference 0–3,65 ng/ml) and IRI at the beginning of fasting test in 104 patients aged 18–80 with suspected NDH. According to results, patients were divided into 4 groups: with insulinoma (group 1; $n=49$), hyperinsulinemic hypoglycemia of other genesis(group 2; $n=12$), hypoinsulinemic hypoglycemia (group 3; $n=13$), withouthypoglycemia (group 4). 10 healthyindividualswereincludedingroup 4 ($n=40$). Each group was divided into subgroups with (A) and without (B) high level of AB-rIRI. In subgroup A we selected subgroup C, in which AB-rIRI level in dynamics (in3,5 months)was determined.
Results
TBIRwasnotrevealed.
High AB-rIRI was revealed in 15.8% ($n=18$) of participants. In group 1 high level of AB-rIRI (Me 4.78 ng/ml [min 3.92; max 10.59]) was confirmed in 39% of cases ($n=7$), in group 2 in 17% ($n=3$; Me 4.16 ng/ml [min 3.77; max 12.3]), in group 3 in 11% ($n=2$; Me 14.84 ng/ml [min 6.46; max 23.21]), in group 4 in 33% ($n=6$; Me 7.97 ng/ml [min 3.68; max 17.26]). Frequency of AB-rIRI carriage in patients with NDH consisted 16% ($n=12$), in group 4–15% ($n=6$). When comparing AB-rIRI levels in subgroups A there were no significant differences ($P=0.52$). AB-rIRI level in all patients of subgroup 1C ($n=4$) was normal after surgery. Insubgroups 2C ($n=1$) and 3C ($n=1$) AB-rIRI levels were high, in subgroup 4C ($n=2$) AB-rIRI levels were significantly higher ($P=0.028$): Me 16.84 ng/ml [min 15.018; max 18.661]. Wecontinuethepatients' observation.
Comparative analysis ingroups 2–4 revealed that in subgroups Aclinical and laboratory signs of insulinresistance occurred significantly more often ($P=0.02$).
Conclusion
The AB-rIRI carriage is not so rare and probably has multi factorial etiology. It is not excluded that patients-carriers are in latent phase of TBIR, so they need careful observation, AB-rIRI'smechanism of action and pathogenesis of formationrequires data accumulation and further study. Given the equivalent increase of AB-rIRI in patients as in healthy individuals, analysis of this parameter in NDH primary diagnosisis inexpedient.
Funding
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AEP315

Time to glycemic control – an observational study of 3 different operations

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Background
Medical treatment fails to provide adequate control for many obese patients with type 2 diabetes mellitus (T2DM). A comparative observational study of bariatric procedures was performed to investigate the time at which patients achieve glycemic control within the first 30 postoperative days following sleeve gastrectomy (SG), mini-gastric bypass (MGB), and diverted sleeve gastrectomy with ileal transposition (DSIT).
Methods
Included patients had a body mass index (BMI) ≥30 kg/m^2; T2DM for ≥3 years, HbA_{1C}>7% for ≥3 months, and no significant weight change (>3%)

within the prior 3 months. Surgical procedures performed were SG ($n=49$), MGB ($n=93$), and DSIT ($n=109$). The primary endpoint was the day within the first postoperative month on which mean fasting capillary glucose levels reached <126 mg/dl. Multivariate logistic regression analysis was used to identify predictors of glycemic control.
Results
The cohort included 251 patients with a mean BMI of 36.04±5.76 kg/m^2; age, 52.84±8.52 years; T2DM duration, 13.09±7.54 years; HbA_{1C}, 8.82±1.58%. On the morning of surgery, mean fasting plasma glucose was 177.63±51.3 mg/dl; on day 30, 131.35±28.7 mg/dl ($P<0.05$). Mean fasting plasma glucose of <126 mg/dl was reached in the DSIT group (124.36±20.21 mg/dl) on day 29, and in the MGB group (123.61±22.51 mg/dl), on day 30. The SG group did not achieve the target mean capillary glucose level within postoperative 30 days.
Conclusion
During the first postoperative month, glycemic control (<126 mg/dl) was achieved following DSIT and MGB, but not SG. Preoperative BMI and postprandial C-peptide levels were independent predictors of early glycemic control following DSIT.

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AEP316

Appropriateness of the 6 mm insulin needle length comparing the glycemic control in overweight-obese and normal weight patients with type 2 diabetes – four years observational study

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Introduction
The length of the insulin needle in last three decades has reduced from 16 mm to 4 mm. The BMI of 10 kg/m^2 difference accounts for a 4 mm difference in subcutaneous tissue thickness. We compared the glycemic control in patients switched from 4 mm needle to 6 mm needle in the Normal Weight (NW) patients (BMI<25 kg/m^2) with the Obese and Overweight (OOW) patients (BMI≥25 kg/m^2)
Methods
We observed 93 T2DM patients (51 females) for the change in HbA1c over a period of four years from Bliss Total Diabetes Care (BTDC) registry from 2016 to 2019. Comparisons were made using ANOVA, Fisher's exact and unpaired *t* test.
Results
The mean HbA1c in the total population at baseline was 9.1% (s.d.±1.9, minimum 5.3, maximum 14, range 8.3, 95% CI 8.7 to 9.5) which significantly reduced to 8.5% (s.d.±2.1, minimum 5, maximum 14, range 8.7, 95% CI 8.1 to 8.9), ($P=0.039$). The mean reduction in HbA1c in the NW ($n=33$) and OOW ($n=60$) was 0.4% (s.d.±1.6, minimum –3, maximum 4.6, range 7.6, 95% CI –0.17 to 0.98) and 0.7% (s.d.±1.8, minimum –3.7, maximum 6, range 9.7, 95% CI 0.27 to 1.2), ($P=0.39$ NS), respectively. We compared the proportions for patients achieving the good glycemic control (HbA1c<7%) in NW ($n=7$) and OOW (19) with inadequate glycemic control in NW ($n=26$) and OOW (41). The association between the glycemic control (target HbA1c<7%), and BMI was not statistically significant ($P=0.33$ NS)
Discussion
The overweight and obese patients achieved a favourable, numerically superior glycemic reduction with 6 mm needle, which would be accounted by the better penetration of the thicker subcutaneous tissue and effectiveness to inject insulin. However, the difference was statistically insignificant which may be attributed due to the chronic progressive nature of diabetes with multiple, unadjusted confounding variables.
Conclusion
We found that longer insulin pen needles may be a better option for their appropriateness and effectiveness in patients with higher BMIs. In order to contribute immensely to the evidence-based decisions of appropriate needle length, the results of our study need corroboration with larger multi-centric studies.

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AEP317

Pancreas-kidney transplantation improves quality of life in type 1 diabetes patients

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Introduction
Diabetes is increasing its prevalence as an enhancement of treatment options arises and mortality declines. Pancreas transplantation has been postulated as one of them, specifically indicated for cases with end-stage renal failure where kidney transplantation is required besides. It has been analysed whether there is a clinical benefit in terms of quality of life (QoL) in patients undergoing pancreas-kidney transplantation (PKT) compared to dyalisis population or other solid-organ transplantation.
Objective
To determine if PKT has a medium-short term impact in QoL in patients with type 1 diabetes mellitus (T1DM) and end-stage renal disease (group PKT) compared to patients with T1DM without end-stage renal disease and indication for PKT (group no-PKT).
Methods and patients
We analysed data from 40 patients admitted in Hospital Universitario Reina Sofía from 2013 to 2018 for simultaneous PKT. We compared them to a random sample of 40 patients suffering from T1DM under insulin treatment for at least 5 years before the study (group no-PKT). Quality of life was assesed using the 36-Item Short Form Health Survey questionnaire (SF-36). Quality of life data were analysed with Mann-Whitney U Test. Continuous cuantitative variables were compared using Student's T Test. Data was analysed using SPSS v. 24.
Results
Patients in both groups showed a similar distribution regarding sex and BMI. No-PKT patients were older than PKT receptors (42.9 vs 38.32 years old, statistically significant). T1DM patients not undergoing PKT had an average duration of the disease of 26.37 years and a HbA1c of 7.92% (63.1 mmol/mol). SF-36 showed a favorable statistically significant ($P<0.05$) impact of PKT when compared to no-PKT group in general health, bodily pain, social functioning, vitality, mental health and health change scales. There were no differences in physical functioning and emotional role SF-36 scales. We observed worse statistically significant ($P<0.05$) results regarding physical role scale in PKT recipients.
Conclusions
1. In our sample, baseline characteristics of patients undergoing PKT are similar to those described in the literature.
2. PKT has a beneficial overall impact in quality of life in patients suffering from T1DM and end-stage renal failure from our sample. However, there are some aspects were we did not find a beneficial result.
3. More studies with a larger sample and follow-up period, prospective data and comparable control groups should be performed in order to confirm these results.

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AEP318

Glycemic control in patients with acute myocardial infarction in an intensive care unit

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Background
Dysglycemia is independently associated with increased risk of death in critically ill adults. The aim of this study was to analyze the differences in glycemic control between the diabetic and non- diabetic patients underwent acute myocardial infarction (AMI).
Materials and methods
Retrospective descriptive study of patients with acute myocardial infarction (AMI) admitted to the intensive care unit (ICU) from January to June 2016, including blood parameters, glycemic treatment, mortality and length of intra hospital stay.
Results
267 individuals with AMI were admitted to the ICUduring the study period. 27.3% of them had a previously diagnosed type 2 diabetes (T2DM) and 10.8% had newly diagnosed diabetes. 50.94% were women and the mean age was 72.36 (s.d. 10.49)/ 69.35 (s.d. 11.9) in diabetics/ non-diabetics. Blood glucose on admission was measured in 79.45% T2DM patients/48.45% patients without T2DM in anamnesis. HbA1c was determined only in 28.8% T2DM patients (mean HbA1c was 6.9%, s.d. 0.93). In diabetic patients

the mean glucose level at admission/during ICU stay – 12.41 mmol/l (s.d. 7.33 mmol/l) /9.94 mmol/l (s.d. 4.57 mmol/l). In 23.3% of diabetic patients more than 80% of blood glucose values fell in the target range from 3.9 to 10 mmol/l. The most common treatment used was sliding-scale insulin 36.9%, sliding-scale+IV insulin 12.3% and IV insulin only in 5.6%.
In non-diabetic patients the mean glucose level at admission/ during ICU stay was 6.72 mmol/l (s.d. 2.27 mmol/l)/6.5 mmol/l (s.d. 1.99 mmol/l). About 30 percent of patients without diabetes develop stress hyperglycemia (SH), 19% of them were treated with insulin (sliding-scale). In only 6.45% of patients with SH achieved 80% of blood glucose values in target range from 3.9 to 7.8 mmol/l. Studies showed that time in targeted blood glucose range from 3.9 to 7.8 mmol/l >80% is associated with survival in critically ill patients without diabetes.
Regarding outcomes, 11.7% of diabetics died versus 9.1% in non-diabetics ($P<0.05$). As to non-diabetic patients in normoglycemic ones intrahospital mortality consists 5.5% vs 35.5% in patients with SH ($P<0.005$).
Conclusion
hyperglycemic patients (both with T2DM and SH) have poorer outcomes after acute myocardial infarction. Our study reviled the insufficient quality of glycemic control in hyperglycemic patients with AMIin ICU. The reason for the poor glycemic control may be the widespread use of sliding scale insulin therapy instead of IV insulin, which is recommended in most international protocols.

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AEP319

Vitamin D supplementation and glucose metabolism parameters in pre-diabetic women

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Objective
To assess glucose metabolism (GM) parameters before and after vitamin D treatment in pre-diabetic women.
Material and Methods
In the study were included fifty eight women with prediabetes (impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)) aged from 40 to 55 with signed informed consent. The study didn't include women with diseases affecting the vitamin D metabolism, as well as women receiving regular vitamin D supplementation. All included women were randomized to two groups: to receive 4,000 IU (group 1, $n=30$) and 500 IU (group 2, $n=28$) cholecalciferol daily for 3 months. At the beginning of the study groups were comparable at age, BMI, HbA1c level. At the baseline and at the end of the study were determined the levels of 25(OH)D and GM parameters including HbA1c, glucose, insulin during OGTT (0, 60, 120 min).
Results
Baseline serum 25(OH)D level was 19.9±8.8 ng/ml, 87.9% of women were insufficient 21 (36.2%) or deficient 30 (51.7%): 28 (93.3%) ingroup 1 and 23 (82.2%) in thegroup 2. After 3 months serum 25(OH)D level increased in all patients (mean 34.3±14.5 ng/ml), however, normalization was detected only in group 1–40.4±14.8 ng/ml. An analysis of GM parameters revealed a decrease in plasma glucose levels at 60' ($P=0.04$) and 120' ($P=0.04$), and reduction in HbA1c level of 6.8% (5,9±0.2% → 5.5±0.2) ($P=0.001$) in women who received 4,000 IU/day. Also, cholecalciferol treatment did not lead to a significant change in fasting insulin level, but was accompanied by an increase in insulin level at 120' by 28.8% (66.7±63.7 → 85.9±3.5) ($P=0.03$) after three months only in group 1. Type 2 diabetes was diagnosed in three (10.7%) women in group 2, while 50% of women had normal glucose level and HbA1c in the group 1 ($P=0.001$).
Conclusion
A dose of 4,000 IU cholecalciferol over three months is associated with a normalization of 25(OH) D level and improved glucose metabolism parameters in pre-diabetic vitamin D insufficient women.

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AEP320

Euglycemic DKA after initiating an SGLT-2 Inhibitor and the P90X diet

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Introduction
We present a case of a patient with type two diabetes mellitus (T2DM) who started empagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor and the P90X diet and presented with euglycemic DKA seven days later.
Case Presentation
A male in his 5th decade of life with a history of T2DM presented for a routine office appointment and had a measured hemoglobin A1C of 9.3. His home diabetes regimen consisted of metformin and sitagliptan. Due to his uncontrolled diabetes, he started empaglifozin 10 mg daily and the P90X diet. One week later, he developed abdominal pain, nausea, and vomiting and presented to the emergency department with an associated 10 pound weight loss. Upon presentation, his serum glucose was 192 mg/dl. Further workup revealed a venous blood pH of 7.09, serum bicarbonate 11 mmol/l (21–32 mmol/l), beta-hydroxybutyrate 10.78 mmol/l (0.02–0.27 mmol/l), anion gap 30 and potassium 4.9 mmol/l (3.5–5.1 mmol/l). He was diagnosed with euglycemic DKA.
Discussion
Euglycemic ketoacidosis, DKA without marked hyperglycemia, is a rare presentation of DKA for type two diabetics. There are multiple reports in the literature of a higher predisposition to euglycemic DKA when taking empagliflozin [1] [2] [3]. It is recommended that any diabetic patient who presents with symptoms of DKA and euglycemia should be evaluated for DKA. Our patient started two treatments for T2DM simultaneously after already taking metformin and sitagliptan. The patient started the P90X diet, a moderate-low calorie (1200–1500 per day), low carbohydrate (approximately 55–90 grams per day) diet and empagliflozin; both of which could leave him prone to ketosis. This case illustrates the need to judiciously treat uncontrolled diabetic patients. Although the patient received standard care, initiating two treatments simultaneously, the P90X diet and empagliflozin, potentially led to euglycemic DKA

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AEP321

Severe insulin resistance with cirrhosis: A case report

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Background
Alstrom syndrome is a rare autosomal recessive genetic disorder characterised by vision loss, hearing loss, childhood obesity, insulin resistance and hyperinsulinemia, type 2 diabetes, hypertriglyceridemia, cardiomyopathy, and progressive pulmonary, hepatic, and renal dysfunction. Hyperinsulinemia develops early, and pancreatic islets show beta-cell proliferation, thus suggesting that both insulin resistance and increased insulin secretion might contribute to glucose intolerance. Increased triglyceride levels, steatosis in the liver and pancreas can also amplify the insulin resistance.
Case presentation
A 20-year-old male patient was diagnosed with congenital amaurosis at the age of 6, diabetes mellitus and hypothyroidism at the age of 8, and hearing loss at the age of 9. Then mutations in ALMS1 detected and Alstrom syndrome was diagnosed. No pathology was detected in bone marrow biopsy for pancytopenia in 2015, and follow-up planned. Chronic liver disease and esophageal varices were detected in 2017. He was admitted to our Endocrinology outpatient clinic with high blood sugar. The serum level of FPG, HbA1c, insulin (fasting), and c-peptide were 148 mg/dl, 10.5%, 63.1 mU/l (3–25) and 5.31 mg/l (0.81–3.85), respectively. Anti-GAD, anti-islet antibody and anti-insulin antibody were negative. He was hospitalised for blood glucose regulation. His height was 155 cm and body weight was 55 kg. On admission, he received 15 units/day insulin glargine and 25 units/day insulin aspart. The total daily insulin requirement increased to 216 units and blood glucose was in the range of 150–300 mg/dl. Due to cirrhosis, the recommendation of pediatric metabolic disease doctors was taken, and then metformin and pioglitazone treatment were started while sodium benzoate treatment was continuing. Liver decompensation did not develop at follow-up and insulin requirement gradually decreased to 160 units/day and blood glucose decreased to 90–190 mg/dl.
Conclusion
In diabetes mellitus types with insulin resistance such as Alstrom syndrome, drugs that increase insulin sensitivity such as metformin and glitazone come into prominence. Due to cirrhosis of our case, metformin and pioglitazone treatment was started cautiously. There was a significant decrease in insulin

requirement and improvement in the brittle blood glucose profile without any side effects.

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AEP322

Switching from liraglutide to dulaglutide, is it worth it?: Outcomes at 24 weeks follow-up

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Introduction
Once-daily liraglutide and once-weekly dulaglutide, both glucagón-like peptide-1 receptor agonists, improve glycemic control and reduce weight in patients with type 2 diabetes mellitus (T2DM) with a similar efficacy according to head-to-head trial AWARD-6. Nevertheless, there is a lack of evidence in a real-world setting. The focus of our study is to assess changes in glycemic control and weight resulting from switching from liraglutide to dulaglutide in patients with T2DM from baseline to week 24 in a real-world cohort of patients.
Methods/Design
Observational and retrospective study carried out in T2DM poorly controlled patients in routine clinical practice. Variables used to assess efficacy were changes in HbA1c, fasting plasma glucose (FPG) and weight from switching to week 24. Changes in antidiabetic drugs for maintaining adequate glycemic control were also recorded. Continuous variables are presented as mean and standard deviation or as a median and interquartile range based on data distribution. Categorical variables are presented as frequencies.
Results
Data from 26 patients (55.5% women; age: 57.4±11.6 years; HbA1c: 7.1 [6.2–8.4]%; duration of T2DM: 12.6±8.7 years) were collected. Failure to achieve metabolic and/or weight targets with liraglutide was the main cause for switching. At week 24, a non-significant reduction of HbA1c (–0.33%; $P=0.09$) and a non-significant increase in weight (+2.53 Kg; $P=0.25$) were observed. FPG was significantly reduced in the whole cohort (–22.3 mg/dl; $P=0.022$) but the difference was non-significant when only patients on insulin, were analyzed. Patients on insulin also, required more insulin units for their glycemic control at week 24 (0.16 IU/kg [0.13–0.17] vs 0.53 IU/kg [0.29–0.93]; $P<0.0001$). Treatment intensification was required in 26.9% of subjects at week 24.
Conclusions
In patients with long-duration T2DM and obesity, switching from once-daily liraglutide to once-weekly dulaglutide doesn't result in beneficial effects in improvement of glycemic control or weight reduction at week 24. Our results, in a real-world setting, are consistent with a previous clinical trial, showing non-inferiority between both treatments. In our experience, there is no efficacy data to recommend switching.

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AEP323

The impact of new technologies on metabolic control in children with type 1 diabetes mellitus during early and middle childhood

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Background
Using new technologies, such as glucose sensors and insulin pumps, may help patients with type 1 diabetes mellitus achieve better glycemic control and quality of life. With the occasion of implementing the National Program for free distribution of continuous glucose monitoring systems (CGMS) starting with January 2019, children aged under 13 years were investigated in order to assess the association between previous use of CGMS and insulin pumps and the metabolic control, evaluated by glycated haemoglobin (HbA1c).

Materials and methods
In this unicentric, cross-sectional study, we evaluated the patients aged less than 13 years, who were admitted to our Department for their first distribution of a fully reimbursed CGMS between January 1st and December 21st, 2019. Patients were divided in 4 groups, according to previous use of a CGMS (CGMS+/CGMS-) or an insulin pump (PUMP+/PUMP-). The group using an insulin pump without using a glucose sensor (CGMS-/PUMP+) was not included in the further analysis because it had only 7 subjects.
Results
The study included 167 patients, 68 girls (40.7%), mean age 9.0±3.0 (range: 2.3–12.9) years, mean diabetes duration 3.8±2.6 years. The CGMS-PUMP- group had 40 subjects, mean age 8.9±2.6 years, mean diabetes duration 3.4±2.6 years, HbA1c 7.9±1.3% (63 mmol/mol). The CGMS+PUMP- had 62 subjects, mean age 9.3±3.2 years ($P=0.55$ vs CGMS-PUMP-), mean diabetes duration 3.4±2.7 years ($P=0.95$ vs CGMS-PUMP-), HbA1c 7.6±1.0% (60 mmol/mol, $P=0.18$ vs CGMS-PUMP-). The CGMS+PUMP+ group had 58 subjects, mean age 8.6±3.1 years ($P=0.6$ vs SENS-PUMP-), mean diabetes duration 4.5±2.4 years ($P=0.028$ vs CGMS-PUMP-), HbA1c 7.3±0.8% (56 mmol/mol, $P<0.01$ vs CGMS-PUMP-). The number of patients using either a CGMS or insulin pump was 127 (76% of the total number of patients)
Conclusions
Children on multiple daily insulin injections using glucose sensors had a similar metabolic control with thosewithout access to a CGMS. However, children using both insulin pump and CGMS had a significantly lower HbA1c as compared with those using none of them. We notice the remarkable high percentage of children using at least one of the technologies that we investigated. In order to achieve the best results, we recommend using the glucose sensors and insulin pumps simultaneously in children aged less than 13 years.

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AEP324

Long-term efficacy and safety of flash glucose monitoring system: 30-month real-life experience

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The use of FreeStyle Libre (FSL) or Flash Glucose Monitoring (FGM) system becomes increasingly popular among people with diabetes, especially type 1 diabetes (T1DM) and several randomized and controlled study have shown how its use is associated with less and shorter hypoglycemic events without deterioration of HbA1c. Nevertheless, there are not yet consistent and lasting data reporting the impact of FGM in people with diabetes in real-life conditions. In this study we evaluated the safety, the acceptance and the efficacy of the FGM system in routine medical practice. In this 30-month prospective observational study we analyzed the glucometabolic data of 656 patients with DMT1 (85%) or insulin-treated DMT2 (15%) (M/F ratio: 1/1; average age 47±15 years; diabetes duration 20.5±13.0 years; MDI 83%; CSII 17%; BMI 26.1±5.1 kg/m^2; total daily insulin dose (TDD) 46±22 IU/day) evaluated every 6 months in our clinic from January 2017 to July 2019. There was a wide diffusion of this type of monitoring and a high percentage of satisfaction (re-prescription rate>97%). Only 3.6% of patients stopped the system and only a quarter of these because they did not consider the system reliable. There was also a rapid and significant improvement in the glycemic control (HbA1c from 7.9±1.3% to 7.6±1.0% with an average reduction of 0.3±1.1% in the first 6 months of follow-up; $P<0.0001$) and this improvement last more than 24 months). This led to a significant increase in the percentage of patients with HbA1c in target (≤7%). This increase was steadily growing throughout the follow-up period from 27.3% at baseline to 41.8% at 24 months ($P=0.005$). We also experienced a lower incidence of severe hypoglycemia and ketoacidosisthroughout the follow up period. However, we did not find any differences in BMI or TDD. The analysis of the Ambulatory Glucose Profile after 6 month showed an inverse relationship between the number of scans and HbA1c ($R=0.243$; $P=0.0032$); estimated HbA1c ($R=0.166$; $P=0.03$), average glucose ($R=0.161$; $P=0.04$) and average duration of hypoglycemia ($R=0.190$; $P=0.01$). There was

instead a direct correlation between daily scans and time in range(TIR) ($R=0.181$; $P=0.02$). Our study shows that the use of FGM is safe (does not increase the risk of severe hypoglycemia or ketoacidosis), effective (early and long-lasting reduction of HbA1c) and represents a valid alternative to self-monitoring of blood glucose.

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AEP325

Evaluation of the effects of phone support programme for patients with type 2 diabetes in treatment with insulin glargine 300 u/ml (T-coah)

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Introduction
T-Coach program is a phone support platform for patients with type 2 diabetes (T2D) treated with insulin glargine 300 U/ml in order to adjust basal insulin dose, reinforce diabetes education and encourage patients to get their goals through regular phone calls. The aim of the study was to evaluate T-Coach program effectiveness in metabolic control and level of satisfaction in patients with T2D.
Methods
We conducted a retrospective, descriptive and observational study that includes patients with T2D enrolled in T-Coach program from October 2016 to October 2019, attending the Endocrinology Unit of Puerta del Mar University Hospital (Cádiz). We analyzed demographic and clinical characteristics, biochemical parameters (fasting glycemia, HbA1c), insulin dose and number of concomitant drugs before, at 3 months and at 6 months after program inclusion. Patient's satisfaction with use of the platform was evaluated.
Results
105 patients were included in T-Coach program. The mean age was 66.96±11.27 years old, with a mean time of evolution of T2D about 13.99±8.17 years. We verified that 56.9% of patients ($n=61$) had microangiopathic complications and 18.6% ($n=22$) had macrovascular complications. Basal insulin dose was 31.01±18.02 U/day and 35.06±20.75 U/day at 6 months. Mean fasting blood glucose levels dropped from 205.19±75.24 mg/dl to 117.1±53.50 mg/dl at 6 months ($P<0.001$). Mean baseline HbA1c was 9.27±1.75% and at 6 months 7.26±1.39% ($P<0.001$). The degree of patient satisfaction was high, with scores above 9/10 on most items evaluated.
Conclusions
In our region, T-Coach program is an effective way to help patients with T2D to reach their optimal insulin glargine U300 dose and improves glycemic control. Majority of patients expressed high satisfaction with the support programme.

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AEP326

Inappropriately elevated serum C-peptide after dosing may interfere with PK and/or PD measurements of study insulin in a euglycemic clamp

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Objective
To examine the relationship between C-peptide levels and endogenous insulin secretion and to understand the effects of elevated C-peptide after dosing on evaluating study insulin and its analogs' PK/PD values in euglycemic clamps.
Method
The study included 33 healthy male volunteers who underwent an 8-h euglycemic clamp with a subcutaneous injection of insulin aspart (0.2 U/kg). Blood glucose (BG), C-peptide, human insulin, and insulin aspart (IAsp) levels were tested at pre-defined time. They were divided into two groups according to C-peptide levels postdosing. Group A: at least one of C-peptide concentrations postdosing was higher than the baseline; group B: C-peptide concentrations postdosing were all below the baseline. The baseline of serum C-peptide was defined as the mean value of –30 min and 0 min predosing. The time profiles of BG, human insulin and C-peptide were recorded, the relationship between human insulin and C-peptide was examined and the factors affect C-peptide were analyzed. IAsp's PK/PD values were collected.
Results
There were 22 in group A and 11 in group B. Baseline BG and CVBG were comparable. The 'clamped' BG was 99.7%±7.1% (group A) and 94.9%±5.1% (group B) of baseline respectively. IAsp's PK values were consistent in two groups while $AUC_{GIR,0-8h}$ was higher in group A than B (1815±551 mg/kg vs 1327±306 mg/kg, $P=0.01$). The C-peptide (308 pmol/l vs 299 pmol/l, $P=0.75$) and human insulin (24.0±7.4 pmol/l vs 29.5±10.2 pmol/l, $P=0.09$) were of no significant difference at baseline but group B had a much lower C-peptide (168 pmol/l vs 309 pmol/l, $P<0.01$) and human insulin (17.3 pmol/l vs 26.0 pmol/l, $P<0.01$) postdosing. The method using C-peptide to predict endogenous insulin secretion had a sensitivity of 85.19% (138/162) and a specificity of 79.20% (316/399). CVBG and the extent of postdosing C-peptide higher than baseline were positively correlated ($r=0.51$, $P=0.01$). The AUC of human insulin higher than baseline decreased with AUC of clamped BG higher than target declining.
Conclusion
Inappropriate elevated serum C-peptide concentrations after exogenous insulin administration indicate insufficient inhibition of endogenous insulin secretion. The BG levels during euglycemic clamp are preferably controlled below the baseline level to sufficiently inhibit endogenous insulin secretion of the subject. The estimated insulin PK values obtained from C-peptide correction method may not be very accurate if postdosing C-peptide level is higher than the baseline.

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AEP327

Metabolic effects of semaglutide after the first months of treatment: A new GLP-1-RA revolution?

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Background
Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1-RA) whose role as a second-line treatment for patients with type 2 diabetes (T2D) has significantly increased. It has demonstrated cardiovascular safety and superiority in terms of glycaemic control and weight loss, compared to other GLP-1-RAs. The most common side effects are mild gastrointestinal, but it may also cause renal failure secondary to dehydration and an increased risk of diabetic retinopathy (DR) complications may be observed in patients with pre-existing DR.
Objectives
To evaluate the effects of short-term treatment with semaglutide, including changes in weight, blood pressure, fasting glucose, HbA1c, LDL-cholesterol, triglycerides and renal function; its safety regarding side effects; and the potential role of semaglutide in the overall improvement of patients with T2D.
Methods
A follow-up study of 38 patients with T2D and obesity (body mass index-BMI>30 Kg/m^2) who started treatment with once-weekly injectable semaglutide in our centre. Data were obtained from the medical records and analysed with SPSS v25.
Results
The mean age of patients was 59.89±9.96 years; 50% were women. Mean T2D disease duration was 14.23±12.39 years, mean HbA1c was 8.27±1.61%, mean BMI was 38±5.7 kg/m^2 and 36.8% of patients had been on a previous GLP-1-RA. Significant improvement were observed at the first follow-up visit after starting semaglutide (79.74±41.3 days) in weight (104.77 vs 108.38 kg; $P<0.001$), BMI (36.7 vs 38.03 kg/m^2; $P<0.001$), fasting glucose (139.13 vs 171.76 mg/dl; $P=0.023$) and HbA1c (7.54 vs 8.27%; $P=0.002$). The potential benefit was higher with optimal/increased doses of semaglutide. A non-significant improvement in LDL-cholesterol and triglycerides was noted. Patients previously treated with another GLP-1-RA experienced no significant changes. However, in patients previously treated with oral antidiabetic drugs (OAD) there were significant improvements in weight (–4.2 kg, $P<0.001$) and HbA1c (–2.95%, $P=0.003$). Regarding therapeutic optimization, we observed a reduction in the required dose of basal insulin (42 vs 46 units; $P=0.05$) in prior insulin users. Adverse events were mild in severity, occurred mainly during the first days/weeks (88.89%), and only two cases required treatment discontinuation.

Conclusions
Semaglutide resulted in significant reductions in HbA1c, fasting blood glucose and body weight during short-term treatment. In addition, adverse events were uncommon. Long-term treatment studies in larger sample populations are required for a better evaluation of this new GLP-1-RA.

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AEP328

The icone study': Multicenter evaluation of the impact of contour next one and contour diabetes app on self-management and adherence in insulin-treated patients with diabetes type 1 or 2

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Objectives
The primary objective was to determine if the use of Contour Next One (CNO) with Contour Diabetes app (APP) was associated with improved self-management using the Summary of Diabetes Self-Care Activities questionnaire (SDSCA). A secondary objective was to establish if CNO and APP together had impact on adherence to self-monitoring blood glucose (BG), indicated by frequency of BG readings and hypoglycemic events. Other secondary objectives were to observe a possible change in HbA1c, patient empowerment and quality of life. Besides satisfaction with the CNO and APP was assessed.
Material and methods
prospective, observational-study in nine clinical practices in Spain. 87 Multiple dose Insulin-treated patients with either type 1 or 2 diabetes mellitus were enrolled. Patients used already the CNO but had not included the APP yet. Patients had a recent HbA1c test and previous 3 month glucose data. Each patient had two on site visits at 0 days (visit 1) and 90 days (visit 2).
Results
84 patients were eligible for the analysis (88.1% type 1; 11.9% type 2). Statistical significant differences were observed in the SDSCA scores for General diet and Specific diet questions with an increase of 1 day of median between visits. Besides a significant increase was observed in the total number of BG readingsbetween visits [median 259.1 vs 276.1] and in the number of readings per day [median 2.9 vs 3.1]. Furthermore, the % of BG values in range was significantly increased in visit 2 [median 51.0% vs 54.0%] and the average of BG values decreased [median 169.0 vs 161.5 mg/dl]. Consequently a significant decrease in the HbA1c value was observed between visits [mean 7.6% vs 7.38%]. On the other hand, there were no significant differences in the % of hypo/hyperglycemic episodes although a trend was observed in visit 2 toward a decrease in episodes >250 mg/dl. No significant differences were found in the questionnaires related to Quality of life and empowerment. The overall satisfaction of patients and Health Care Practitioners with CNO and the APP scored high.
Conclusion
The effects of the joint use of CNO and the APP are already observed after a relative short period in multiple dose insulin-treated patients with diabetes type 1 or 2. The CNO with the APP helped the patients to have a better glycemic control by means of improving their adherence to self-monitoring and diet self-management, all without reducing their quality of life or empowerment.

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AEP329

Experience of using insulin therapy with the closed loop method among patients with type 1 diabetes mellitus in Russia

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The aim
To evaluate the efficiency and safety of using closed loop systems in patients with type 1 DM living in Russia.
Results
88 respondents (or those legal representatives) with type 1 DM in insulin therapy by closed loop systems, members of Russian-speaking community, were included to the study. 90% of respondents living in Russia. All respondents using do-it-yourself artificial pancreas systems (DIYAPS): Loop (19.3%), Open APS (30.7%) and Android APS (50%). Hlycated haemoglobin was normal in 90% of cases of using DIYAPS. 89% of respondents notice improvement of glycemic control. Among the advantages of closed loop therapy, respondents noted an increase time-in-range (78% of respondents), a decrease in the frequency of mild hypoglycemia (61% of respondents), a decrease in the frequency of severe hypoglycemia (59% of respondents), and improved glycemic control at night (86% of respondents) .
Conclusions
The use of pump insulin therapy using closed loop systems leads to a decrease in the level of glycated hemoglobin by 0.5% ($P=0.01$) compared with the use of standard pump insulin therapy. The majority (78%) of type 1 DM respondents receiving closed-loop pump insulin therapy noted an increase in the time-in-range compared to standard pump insulin therapy. The use of closed-loop systems is associated with a decrease in the frequency ofmild (in 61% of respondents) and severe hypoglycemic conditions (in 59% of respondents) compared to standard pump insulin therapy in respondents with type 1 DM.

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AEP330

Use of statins and cognitive performance in elderly type 2 diabetic patients

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Background
Type 2 diabetes (T2D) is known as risk factor for mild cognitive impairment (MCI), which can lead to confirmed dementia. T2D patients often take statins for cardiovascular prevention but, nowadays, it is not clear if these drugs could also prevent cognitive impairment.
Objective
We aimed to evaluate the association between statins in primary or secondary cardiovascular prevention and cognitive performance in old T2D patients referring to our Internal Medicine offices.
Material and method
We enrolled 40 consecutive, over 60 years, T2D patients (average of 75±6 years), nine females and 31 males, all affected by essential hypertension.
Patients affected by major adverse cardiovascular events or confirmed dementia were excluded. We registered anthropometric data (BMI 27.1 kg/m^2) and evaluated major cardiovascular risk factors as pulse blood pressure (PBP) and all patients underwent *Montreal Cognitive Assessment* (MoCA), a MCI screening test and *Frontal Assessment Battery* (FAB) for the screening of executive functions impairment. Both tests were corrected for school grade and FAB also for age.
Results and conclusion
21 patients taking statins got higher MoCA and FAB scores (respectively +17%, $P=0.015$ and +15%, $P=0.048$), higher pulse PBP (73±17 vs 64±11 mmHg, $P=0.046$), and lower LDL levels (59±29 vs 85±34 mg/dl, $P=0.036$) if compared with patients not taking these drugs. MoCA score was directly correlated to age ($r=0.329$, $P=0.038$), while considering FAB no other significative correlation was found. Even considering potential confounders as age, sex, BMI, DBP and HbA1c, taking statins still remains associated to MoCA scores ($\beta=0.466$, $P=0.002$). To sum up, elderly T2D patients taking statins have a better cognitive performance compared with patients with same age and disease profile not taking this pharmacological class. Future treatment trials could explore the role of preventive therapy with statins in cognitive impairment development.

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AEP331

Clinical and metabolic benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i) therapy in diabetic patients with psychiatric comorbidities

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Introduction
Sodium-glucose cotransporter 2 inhibitors (SGLT2i) therapyhas proven effective in type 2 diabetes but there is little data on its effect in patients with psychiatric comorbidity, who usually present worse metabolic and clinical control. The aim of this study was to evaluate if there are differences in the effect of this therapy in relation to the presence of these pathologies.
Methods
225 patients included in a therapy protocol with SGLT2i, 54.9% men, mean age 63.7±10.0, time of evolution of diabetes 11.1±9.0 years, were evaluated analyzing the changes in clinical and biochemical parameters at baseline and after one year of therapy with SGLT2i. The analysis was performed in the global and separating in two groups according to the presence of psychiatric comorbidity. Quantitative variables are expressed by mean (standard deviations). Qualitative variables are expressed by frequencies and percentages. Paired samples T-test are used in the statistical analysis. We consider significant $P<0.05$.
Results
24.4% of patients presented psychiatric comorbidities, and the most frequent diagnoses were anxiety (34.5%), depression (32.7%) and anxiety-depressive syndrome (16.4%). Baseline data and after follow-up expressed as means (s.d.) and means difference (s.d.) (95% CI): weight (kg) 91.2±19.7 vs 87.9±19.1; 3.4±5.1 (2.6 to 4.2) ($P<0.001$), body mass index (kg/m^2) 34.5±6.2 vs 33.3±6.1; 1.2±2.1 (0.9 to 1.6) ($P<0.001$), glycated hemoglobin (%) 8.2±1.2 vs 7.4±1.1; 0.7±1.2 (0.5 to 0.9) ($P<0.001$), glucose (mg/dl) 169.6±69.3 vs 143.5±46.3; 26.2±73.5 (14.7 to 37.6) ($P<0.001$), systolic blood pressure (mmHg) 149.9±17.8 vs 144.0±18.8; 5.9±20.2 (2.5 to 9.3) ($P=0.001$), diastolic blood pressure (mmHg) 84.0±11.3 vs 82.0±10.7; 2.0±10.2 (0.3 to 3.7) ($P=0.024$), high-density-lipoprotein cholesterol (mg/dl) 45.3±11.9 vs 48.8±13.7; 3.5±11.4 (5.3 to 1.6) ($P<0.001$), triglycerides (mg/dl) 189.0±102.5 vs 160.7±77.8; 28.4±94.0 (13.6 to 43.1) ($P<0.001$), glomerular filtration rate (ml/min/1.73 m^2) 82.6±34.0 vs 88.2±24.5; 5.6±26.8 (9.9 to 1.3) ($P=0.01$). There were no significant changes in total cholesterol, low-density-lipoprotein cholesterol and albuminuria. In the separate analysis we found no significant differences regarding the benefit in patients who had psychiatric comorbidity.
Conclusions
Psychiatric comorbidity in diabetic patients is associated with worse results of some pharmacological treatments, probably due to a loweradherence to changes in lifestyle. In our study, SGLT2i therapyoffers the same advantages in terms of metabolic and clinical control in this group of patients

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AEP332

Immune checkpoint inhibitors (ICIs) and 'Fulminant Diabetes': Two emblematic cases

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Context
Programmed cell death protein 1/programmed cell death protein ligand 1 (PD-1/PD-L1) are key regulators in T-cell activation and tolerance. Nivolumab (PD-1 inhibitor) and Atezolizumab (PD-L1 inhibitor) are monoclonal antibodies approved for the treatment of several types of advanced cancers. Immune checkpoint inhibition caused by these drugs can result in immune-related adverse events (irAEs) New-onset diabetes mellitus has been reported in fewer than 1% of patients and is a rare but life-threatening irAE, which is often characterized by rapid-onset hyperglycemia and ketoacidosis, with low levels of endogenous insulin secretion. Here we report two cases of new-onset diabetes associated with anti-PD-1 and anti-PD-L1 therapy that showed a rapid fall into insulin-dependence.
Case 1
A 60-year-old man received Atezolizumab for metastatic lung adenocarcinoma. After two doses, he developed hyperglycemia, requiring basal-bolus insulin therapy. After the fourth dose, the patient was admitted to our Departement because of severe weakness, nausea, abdominal pain, and dizziness. Laboratory tests revealed severe hyperglycemia with ketoacidosis, low levels of c-peptide, hyperkalemia, and hyponatremia. Islettyrosine phosphatase 2(IA2) antibodies and anti-glutamic acid decarboxylase (GAD) antibodies were undetectable. Further investigations revealed the DRB1*04 and DQB1*03 haplotypes, which are usually associated with increased susceptibility to T1DM. After resolution of ketoacidosis, due to persistence of mild hyponatremia and hyperkalemia, an adrenal dysfunction was suspected. The evaluation of HPA-axis revealed the presence of a Primary adrenal insufficiency with 21OH –hydroxylase antibodies positivity
Case 2
A 43-year-old woman, affected by a malignant skin melanoma, was treated with nivolumab. After the second cycle, she was diagnosed with transient thyrotoxicosis followed by autoimmune hypothyroidism, requiring replacement therapy with levothyroxine. After the sixth cycle, severe ketoacidosis arose, which required insulin therapy. Antibodies against pancreatic beta cells antibodies were negative. HLA typing revealed DQB1*02; DQB1 *0602; DQA1 *0102 haplotypes that are not usually associated with increased susceptibility to T1DM.
Conclusion
ICIs related 'fulminant diabetes' is a rare but potentially life-threatening irAE that manifests with severe ketoacidosis and needs to be diagnosed timely and managed properly. After the first manifestation of ICIs-related diabetes, the beta-cell function is usually permanently impaired, resulting in a long-term need for insulin injection.
Moreover, fulminant diabetes can manifest in the context of an autoimmune polyglandular syndrome, as described in our 2 cases. The coexistence of ketoacidosis and adrenal crisis, although rare, represents an extremely severe combination of iRAEs.

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AEP333

Vitamin B12 levels and its association with glycaemic control and pregnancy outcomes in women with gestational diabetes

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Introduction
Data on Vitamin B12 deficiency and its relationship with Gestational Diabetes Mellitus (GDM) andpregnancy outcomes are limited. The aim of the present study is to determine, in pregnant women with GDM, the association between Vitamin B12 levels and glycemic control, as well as with pregnancy outcomes.
Methods
We studied 44 women with GDM, mean age 31.9±5.8 years old, at the second trimester and at labor and measured weight, height, body mass index (BMI), HbA1c, Vitamin B12 (B12) and folic acid (FA) levels, as well asthe gestational age at delivery (GAd), childbirth type and offspring birthweight (of BW).
Results
Baseline mean gestational age was 26.3±7.3 weeks, mean mother weigh, BMI and HbA1c were 80.17±17.07 kg, 29.89±6.11 kg/m^2 and 5.1±0.3% respectively. Mean B12 and FAlevels were 241.80±122.04 pg/ml and 13.67±6.58 ng/ml respectively. 28 out of 44 women had normal B12 (63.63%, NB12), 16 out of 44 had B12 deficiency (LB12) (36.36%, B12<150 pg/ml) and 13 of the LB12 had adequate FA levels. There was no relationship between B12 levels and HbA1c ($r=-0.025$, $P=0.874$), and B12 levels and BMI ($r=-0.128$, $P=0.419$). NB12 women gave birth to 15 females and 13 males, 16 (57.14%) by caesarean section, mean GAd was 38.18±0.94 weeks and mean of BW was 3220±380 gr. LB12 women gave birth to 11 females and six males (one twin pregnancy), 7 (43.75%) by caesarean section, mean GAd was 37.93±2.43 weeks and mean of BW was 3059.38±658.35 gr. In both LB12 and NB12 there was no relationship between B12 and GAd ($r=0.185$, $P=0.493$ and r=–0.141, $P=0.473$

respectively), between B12 and of BW (r=0.232, P=0.387 and r=–0.112, P=0.569 respectively) and B12 and child birth type.
Conclusion
A significant percentage of pregnant women with GDM had B12 deficiency. B12 deficiency, does not seem to have any associationwith either the glycemic control and the body mass index of the pregnant women, or with gestational outcomes. More studies with a larger number of participants are needed to confirm these findings.

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AEP334

Abstract withdrawn

AEP335

Study on lipid compositions of the skeletal and liver tissues in animals with the induced alimentary obesity and insulin resistance

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Obesity is thought to be a main risk factor of insulin resistance and diabetes mellitus. Study on concentrations of lipids in the tissues of animals with experimental model of obesity resulting in insulin resistance remains currently central. The work was initiated to study the spectrum of lipids and their concentrations in the tissues of experimental animals with the induced alimentary obesity.
Alimentary obesity with concurrent insulin resistance was induced in the outbred rats by means of a 6-month high-calorie carbohydrate diet. The thin-layer chromatography was used to determine the spectrum of lipids (Kates, 1975); neutral lipids were measured spectrophotometrically (Prokhorova, 1982), while phospholipids were measured by phosphorus (Vaskovsky *et al.*, 1975).
The model of obesity and insulin resistance induced, body mass and body fat mass of rats was found to increase by 62% and 6.2%, respectively. The blood glucose and cholesterol were found to increase, but insulin sensitivity of some tissues declined. As to lipid composition in the skeletal muscle of animals with alimentary obesity, lysophosphatidylcholine (LPC), phosphatidylethanolamine (PE) and cardiolipin were found toincrease by 18%, 17% and 10%, respectively, whilesphingomyelin (SPH), phosphatidylcholine (PC), phosphatidylinositol (PI) and phosphatidylserine (PS) reduced by 41%, 24%, 17% and 39%, respectively; total phospholipids were found to decrease by 16%. In the liver tissues of rats with alimentary obesity, lysophosphatidylcholine (LPC), cardiolipin and phosphatidic acid (PA) were observed to reduce by 280%, 7% and 29%, respectively, while LPC, PC, PI and PS were found to decrease by 31%, 24, 3% and 5%, respectively. The increase in LPC and PA in the tissues under study could be the evidence for activation of phospholipases taking place in alimentary obesity. The neutral lipids, such as cholesterol, non-esterified fatty acids and total lipids were established to increase by 33%, 60% and 22%, respectively, in the skeletal muscle, and by 23%, 49% and 17% in the liver tissues, respectively
Our findings demonstrated that in the alimentary obesity model with the increased blood glucose and cholesterol there are changes in lipid composition of the insulin sensitive tissues. The changes are likely to produce an effect on the receptor sites of insulin in the tissues under study and cause the onset of insulin resistance.

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AEP336

Studying the care and social pathway of young adults with endocrine and metabolic diseases during transition: The 'Transend' cohort

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Context
The transition period between pediatric and adult medicine is associated with poor patient outcomes and an important number of patients lost to follow up. Intervention exist but the few published randomized trials do not allow to study long-term patient outcomes nor intervention sustainability in time. Objective. Describe the cohort of patients in adult care who benefit from a new transition program based on case management approach, its activity and follow-up outcomes.
Methods
A longitudinal study was led since September 2016 in adult services of endocrinology, nutrition and diabetology of a French University Hospital. Patients with any endocrine disease diagnosed during childhood and transferred to adult care were included. The care pathway for these patients was built in three steps. Step 1 is dedicated in liaising with pediatric services and patient to facilitate its first visit in adult care. Step 2 defines the care pathway in adult service based on the needs assessment realized by the coordinator upon the patient's arrival in adult service. Step 3 focuses in liaising with structures outside hospital (GP, educational and social sector). Thorough the follow-up, the coordinator is identified as the key contact by the patients. Attendance to medical appointments, clinical, and social data are collected throughout patient follow-up.
Results
Since 3 years, 500 patients benefited from the case management mainly for their obesity (n=91, 18%), type 1 diabetes (n=54, 11%), malignant brain tumor (n=68, 14%) or congenital hypopituitarism (n=42, 8%). They were aged 19 in median at transfer in adult care, sex ratio : 0,5. A large majority live in the parental home (409, 82%), 169 (34%) are university students, 130 (26%) are in high school, 90 (18%) are in medico-social institution. Patients who required most of support from the coordinator usually combine one (or more) somatic disease and either a neuro-cognitive disorder or a psychiatric disorder, they all have social difficulties. In patients with more than 3 months of follow-up (median : 18 months), 22/418 (5%) are out of follow-up. Concerning the patients for whom the follow-up is 36 months or more, the percentage of out of follow-up is the same: 5%.
Conclusions
The case manager addresses the complex needs of diverse patients. With time, the cohort will provide unprecedented long-term results of patients with various conditions who went through transition.

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AEP337

The complexity of associations between type 2 diabetes mellitus and comorbidities in multimorbid population in Lithuania

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Introduction
Diabetes is one of the most common chronic diseases in multimorbid population and one of the most frequently detected conditions in multimorbid disease clusters. Approximately 40% of diabetic patients have three or more coexisting chronic conditions.
Aim
To assess the frequency (percentage) of chronic conditions co-occurring with diabetes in multimorbid Lithuanian population.
Methods
Database fromthe Lithuanian National Health Insurance Fund under the Ministry of Health covering the period from 2012 till 2014was used. We exploited a reduced chronic diseases list with the diagnostic codes of ICD-10-AM (I11; I20; I25; I50; I48; E11; E06.3; E89; J44; J45; M05; M15-M19; M80; M81; M54; G54; G55). A series of heat maps for co-occurrence of 17 (diabetes included) chronic conditions were developed. Heat maps were stratified by age and gender to displaythe frequencies of chronic conditions

dyads. Chronic conditions were included into the heat maps if the frequency of co-occurrence with type 2 diabetes mellitus (E11) was 10% and more.
Results
Data of 103367 patients with diabetes (63.0% female) were analyzed. Hypertensive heart disease (I11) and angina pectoris (I20) were the most common chronic conditions associated with E11 for both genders in all age groups. I11 varied from 61.4% to 77.3% and from 84.5% to 91.1% with the highest frequency of 77.3% in the 60–69 years age group and 91.1% in the same age group in female and male respectively. Meanwhile I20 varied from 13.4% to 38.1% and from 21.7% to 50% with the highest frequency of 38.1% in the 70–75 years age group and 50% in the same age group in female and male respectively. Atrial fibrillation and flutter (I48) co-occurred with E11 earlier in male (50–59 years age group) than in female (70–75 years age group). Chronic obstructive pulmonary disease co-occurred with E11 only in male group and ranged 13.1% in the 70–75 years age group.9 chronic conditions were associated with E11 only in male, age groups of 50–59 and 70–75 years.
Conclusions
The most commonly associated conditions with diabetes were hypertensive heart disease and angina pectoris. There were differences in gender: chronic obstructive pulmonary disease was associated with diabetes only in male and atrial fibrillation and flutter co-occurred with diabetes earlier in male than in female. The number and frequencies of associations increased with age in both gender groups.

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AEP338

Lipoprotein (a) in patient with type 2 diabetes mellitus and healthy subjects

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Backgroud
Increased lipoprotein (a) {Lp(a)} concentrations are associated with cardiovascular disease. Whether type 2 diabetes increase the level of Lp(a) still controversial. We studied the level of Lp(a) in health and type 2 diabetes Thai subjects and studied the relationship between Lp(a) and metabolic factors in both groups
Methods
The study included 180 normal glucose tolerance healthy subjects that have age and sex matched with 180 type 2 diabetes patients. All participants were fasting for 10–12 hours at night and have blood samples for Lp(a), total cholesterol, triglyceride, HDL-C, LDL-C, BUN, Cr, FBS, HbA1c. Lp(a) was measured by rate nephelometry methods with the immunochemistry systems. The coefficient of variance of Lp(a) were 3.4 and 6.4% for intra and interassay variability, respectively.
Results
The mean age of diabetic subjects was 60.8±11.5 years and 55% was male that were not statistically different from the healthy control. All subjects had blood creatinine level less than 2 mg/dl. Mean HbA1c of diabetes subjects was 7.5±0.9%. The mean Lp(a) level was 23.6 mg/dl in control and 22.8 mg/dl in diabetes subjects that is no statistically different (NS). The median Lp(a) was 16.3 and 14.0 in control and diabetes subjects respectively (NS). The percentage of subjects who had Lp(a) more than 30 mg/dl was 26.1% and 25.0% in control and diabetes subjects respectively (NS). The total cholesterol and LDL-C level are no statistically different between control and type 2 diabetes subjects. The diabetes subjects had higher triglyceride level than control (156.6±69.1 vs 126.8±39.7 mg/dl) and lower HDL-C level than control (42.8±12.4 vs 52±12.8 mg/dl). The correlation between log Lp(a) and other factors include age, sex, lipid profile, fasting plasma glucose, HbA1c and creatinine was studied by spearman rank in both diabetic and control subjects. There was significant negative correlation with serum triglyceride in both diabetes and normal subjects and there was only significant positive correlation with HDL-C cholesterol in healthy subjects. The other factors were not significant correlated with log Lp(a).
Conclusions
Lp(a) level in type 2 diabetes were not different from healthy subjects. Lp(a) in both type 2 diabetes and healthy subjects had negative correlation with serum triglyceride level.

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AEP339

Correlation between BMI and cognitive performance in type 2 diabetic patients

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Background
The association between diabetes (DM) and cognitive impairment is already well established. DM affects multiple superior domains, *in primis* working memory and executive functions and damages nervous system in both morphological and functional ways. The *Montreal Cognitive Assessment*(MoCA) is a neuropsychological test defined as the best tool evaluating mild cognitive impairment (MCI) in DM.
Objective
Our study aimed to investigate a correlation between anthropometric variables and *MoCA*scores in an adult cohort of type 2 diabetic patients referring to our Internal Medicine offices between November 2018 and April 2019.
Material and methods
We excluded subjects affected by diagnosed dementia, brain trauma or injuries, major adverse cardiovascular events during the previous 6 months or portal-systemic encephalopathy. We recruited 40 *over* 60 (75±6.06 years) patients and collected their anthropometric, clinical and laboratory data and then they underwent *MoCA* testing, which score was corrected by school grade. In order to exclude *MCI*, minimum score was of 26.
Results
Participants had a *MoCA* average score of 21.6 (±4.7) over 30. Recall memory resulted the most affected cognitive domain (average 32%), while space-time orientation the least (average 96.7%). Although our cohort was limited by number, a significative statistic correlation between BMI and *MoCA* score emerged (r 0.329). We registered a progressive neuropsychological score increase with increasing BMI considering our population divided in tertiles by MoCA results, which was biologically significative according to the well-known *obesity paradox*. This correlation was confirmed even after correction for sex, age and years of diabetic disease.

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AEP340

Prevalence and prognosis impact of diabetes in cirrhotic patients

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Introduction
The prevalence of diabetes increases during cirrhosis resulting from a significant alteration in carbohydrate metabolism modifying the management of diabetes and worsening the liver prognosis. The aim of this work is to determine the prevalence of diabetes during cirrhosis, and to assess its prognostic impact on the disease.
Material and method
this is a study collecting all cirrhotics followed in the gastroenterology department over a period of 4 years. We divided the patients into 2 groups: G1: diabetic patients and G2: non-diabetic patients.
Results
A total of 71 patients with a mean age of 62 years (25–83 years), were collected. Viral origin was the most common cause (40.8%). The prevalence of diabetes was estimated at 45.07% (n=32). The factors associated with diabetes were: advanced age (age> 60, P=0.04), presence of another criterion of metabolic syndrome (P=0.001), viral etiology C (P=0.045) and a disease classified Child–Pugh B (P=0.04). Stage C was more frequent in group 1 patients with no significant difference (31.25% vs 28.2%, P=0.4). There was no significant difference between the 2 groups regarding gender. In addition, there was no difference between the 2 groups concerning the risk of occurrence of complications of cirrhosis (oedemato-ascitic decompensation, refractory ascites, digestive hemorrhage due to varicose vein rupture, ascites fluid infection and hepatic encephalopathy) apart from hepatocellular carcinoma which was more frequent in group 1 without significant difference (29.03% vs 15.38%, P=0.1).
Conclusion
The prevalence of diabetes during cirrhosis is quite high. This requires special attention for therapeutic management and constitutes a negative prognostic factor aggravating the state of the liver.

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AEP341

Anti-Lipogenic effects of cabergoline: A molecular study on white adipocytes

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Obesity is caused by an imbalance between dietary energy intake and expenditure. The expression of dopamine receptors (DRs) in human adipocytes has been already demonstrated. Moreover, the effects of cabergoline, a dopamine agonist, on body weight and glucose homeostasis in obese subjects without hyperprolactinemia has already been reported. The current study investigates the effects of cabergoline on lipid accumulation and on adipogenic factors expression to better define the pivotal role of dopaminergic system in obesity etiology. To this purpose, 3T3-L1 cells, the most-well established mouse model for adipogenesis in *in vitro* studies, were used. Proliferating 3T3L1 cells were suitably differentiated in mature adipocytes and mRNA levels of DRs were monitored during the differentiation process by RT-qPCR. Moreover, effect of escalating doses of cabergoline (10^{-8} M and 10^{-6} M) alone or combined with 2×10^{-8} M insulin, on lipid accumulation were investigated through Oil Red O staining after 3 days of treatment. To confirm the anti-lipogenic action of cabergoline, mRNA and protein levels of adipogenic factors were measured by RT-qPCR and WB analysis respectively. Intracellular analysis of pAMPK Thr172 and pAKT Ser473 was performed to confirm anti-lipogenic action of cabergoline by inducing fat β-oxidation process.
3T3-L1 showed increased DRs mRNA levels during differentiation, concomitantly to insulin receptor, with maximum expression levels at day 12 of differentiation. Quantitative measurement of the intracellular oil droplet revealed that after cabergoline 10^{-8} M and 10^{-6} M, alone and with 2×10^{-8} M insulin, the lipid content decreases by about 60% compared to control ($P<0.0001$). Besides, cabergoline 10^{-8} M and 10^{-6} M alone and with 2×10^{-8} M insulin significantly down-regulates leptin gene expression compared to control ($P<0.001$). While gene expression of adiponectin and PPARγ remains unchanged after treatment, protein levels of bothare inhibited after 3 days of exposure with cabergoline 10^{-6} M alone and with a stronger inhibition when cabergoline was combined with 2×10^{-8} M insulin. Inhibition of fatty acid synthase and pAKT Ser473 protein expression and activation of pAMPK Thr172 after cabergoline 10^{-6} M alone or combined with 2×10^{-8} M insulin confirm that cabergoline can reduce *de novo* synthesis and accumulation of lipids by stimulating fat β-oxidation.
In conclusion, these data demonstrated a novel role of cabergoline in the suppression of lipid accumulation by reducing adipogenic- and fatty acid synthesis-related factors expression in mature 3T3-L1 cells. The combination with insulin can increase this effect providing the basis for a novel research addressed to anti-obesity use of cabergoline.

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AEP342

Modification of standard thresholds improves performance of noninvasive scores of liver fibrosis in patients undergoing bariatric surgery

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Background
In bariatric surgery (BS) patients, nonalcoholic fatty liver disease and fibrosis are present in up to 90% and 24%, respectively. Several fibrosis risk scores have been developed and have been validated in cohorts different from morbid obesity (MO). We aimed to determine whether established liver fibrosis scores were accurate in predicting fibrosis in MO subjects.
Material and methods
Cross-sectional analysis in a cohort of MO patients undergoing BS in a Hospital in Spain over a 2 – year period. Demographics, anthropometric, clinical and laboratory features were assessed. The APRI, FIB-4, Forns, NAFLD-fs, BARD, BAAT and Hepamet fibrosis scores were calculated.
Liver biopsies were performed during BS. The NAS score and Kleiner scale were used to assess steatohepatitis (NASH) and fibrosis, respectively.
Student *t*-test, Fisher-Pitman, Pearson's chi-squared or Fisher's exact tests were used. A $P<0.05$ was considered significant. The AUROC was calculated, as well as measures of diagnostic accuracy based on established thresholds. Modified cutoff values for differentiating F2–4 (SF: significant fibrosis) disease were calculated. Logistic regression analysis was performed to find predictors of significant fibrosis.
Results
50 patients were included. Nine participants (18%) had SF. Sixteen (32%) had NASH. Proportion of patients with NASH was higher in the SF group (88.9 vs 19.5%, $P<0.05$). BMI, HbA1c, ALT, AST an GGT levels were significantly different in patients with SF. Basal glucose, HbA1c, AST and GGT were identified as independent predictor of SF.
APRI, FIB-4, Forns and Hepamet fibrosis scores were significantly higher in the SF group ($P<0.05$). When thresholds were modified to optimize detection of significant fibrosis, they were considerably lower than those described in the literature, this allowed to identify a greater proportion of fibrosis, improving sensitivity and consequently increasing negative predictive value (NPV).
BARD (AUC 0.76) and Forns (AUC 0.67) scores had the best performance considering the cutoff suggested by the ROC analysis, both with sensitivity of 88.9%, specificity of 51.2%, NPV of 95.5% and efficiency of 58%, which makes them appropriate to exclude fibrosis.
Conclusions
Basal glycemia, HbA1c, AST and GGT are independent predictors of SF in our population. Existing scoring systems are unable to stratify fibrosis risk in MO patients using established threshold. It is necessary to modify these cutoffs to improve accuracy. By doing so, the BARD and the Forns scores had a good global performance with NPP of 95.5% and permits to predict the absence of SF.

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AEP343

Effects of bariatric surgery on heart rhythm disorders: A systematic review and meta-analysis

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Background
Obesity is associated with cardiac structural changes, repolarization abnormalities and rhythm disorders. The aim of this systematic review is to provide an overview of the literature on obesity, cardiac arrhythmias, obesity associated ECG abnormalities and the effects of bariatric and metabolic surgery.
Methods
A systematic search on the effects of obesity and bariatric surgery on cardiac arrhythmias and associated ECG abnormalities was conducted. The methodological quality of the included studies was rated using the Newcastle-Ottawa scale (NOS) for non-randomized trials. The agreement between the reviewers was assessed with Cohen's kappa.
Results
Fourteen studies were included with a methodological quality ranging from poor to good. The agreement between the reviewers, assessed with the Cohen's kappa, was 0.75. Majority of the studies showed a significant decrease of QT interval and related measures after bariatric surgery. Regarding atrial fibrillation the results were conflicting. Seven studies were included in the meta-analysis on effects of bariatric surgery on QTc interval and a significant decrease in QTc interval of –33.62 ms (95% CI: –49.767 to –17.446) was seen. Similar effects were seen after bariatric surgery regarding P-wave dispersion and showed a significant decrease after bariatric surgery (–12.87 ms (95% CI: –17.739 to –8.004)).
Conclusion
Obesity is associated with prolongation of QTc interval, lengthening of P-wave and QTc dispersion and also with rhythm disorders like atrial fibrillation. Significant weight loss by bariatric and metabolic surgery results in a significant decrease in QTc interval and P-wave dispersion. The effects on atrial fibrillation are conflicting and not yet fully understood.

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AEP344

Physical activity is associated with lower arterial stiffness after the menopause: The effect of BMI

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Introduction
Metabolic syndrome and cardiovascular disease (CVD) are well-known long-term implications of the menopausal transition. Lifestyle practices like exercise could potentially act protective with regards to future cardiovascular risk at midlife. We aimed to assess the impact of physical activity on the development of subclinical CVD in postmenopausal women, adjusting for the effect of underlying obesity.
Methods
This cross-sectional study from a University Menopause Clinic evaluated a total of 623 apparently healthy postmenopausal women. Anthropometric parameters were evaluated, and women were classified into normal weight [body mass index (BMI) ≤25 kg/m^2 $n=194$] and overweight-obese (BMI >25 kg/m^2, $n=431$). Fasting blood samples were obtained to assess biochemical and hormonal profile. Sonographical assessment was performed immediately thereafter including functional [pulse wave velocity, (PWV)] and structural markers [intima media thickness (IMT) and atherosclerotic plaques presence] of subclinical vascular disease. Main outcome measures consisted of the extent of subclinical CVD according to severity of physical activity and the potential confounding effect of obesity.
Results
In the total sample, mean values of PWV differed according to the intensity of physical activity (sedentary vs walking vs moderate vs vigorous: 9.07±1.22 m/s vs 9.12±1.72 m/s vs 8.47±1.31 m/s vs 7.94±0.40 m/s, ANOVA *P*-value for linear trend 0.003). Physical activity of moderate intensity is associated with lower levels of PWV (b-coefficient=–0.126, *P*-value=0.001), adjusting for age, menopausal age, BMI, lipids, insulin resistance, smoking, blood pressure. This was not the case for walking or activity of severe intensity. Overweight-obese vs normal weight women had higher levels of common carotid artery (CCA) IMT (13.8±1.0 mm vs 13.3±1.5 mm, *P*-value=0.005), greater PWV (9.1±1.5 m/s vs 8.4±1.5 m/s, *P*-value<0.001) and higher frequency of plaques in CCA (54.9% vs 30.6%, *P*-value <0.001). In the subgroup analysis, the association between physical activity and PWV remained significant only for women with normal weight but not for overweight-obese participants.
Conclusion
Physical activity seems to be related with a protective effect on the extent of subclinical CVD in postmenopausal women. Exercise of moderate intensity is linked with lower levels of PWV after the menopause, an effect mainly pronounced in normal weight women.

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AEP345

Role of an automated screening tool in familial hypercholesterolemia

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Familial hypercholesterolemia (FH) remains underdiagnosed in general population. Screening programs in unselected individuals have shown modest results in identifying patients with FH. Incidence of FH is higher in young patients with coronary artery disease (CAD), especially when associated with high LDL-cholesterol levels. Targeted screening in this population could add value to FH-index patient identification. We have established an IT-based automated screening tool to enhance diagnostics, treatment and cascade screening of FH.
Objectives
To assess if an automated screening tool would provide additional support in recognition of potential FH-patients.
Methods
The study is based on the data collected from consecutive patients undergone coronary angiography in the Heart Hospital at Tampere University Hospital between 2007 and 2017 and fullfilling the criteria of the automated screening tool, i.e. premature CAD verified in angiography (men<55 years and women<60 years) and history of high total (>8 mmol/l) or LDL-cholesterol (>5 mmol/l) level. Health records were analyzed to determine if patient had diagnosis of FH prior to CAD diagnosis, if they were diagnosed for FH based on clinical criteria after CAD, if genetic testing had been conducted and if cascade screening had been initiated.
Results
The automated screening tool identified 211 patients from 28.295 angiographies that fullfilled the criteria. After excluding patients with apparent secondary hypercholesterolemia 162/211 (77%) patients were included in further assesment regarding FH. A total of 107 (66%) patients had probable/definite FH and 55 (34%) had possible FH based on the DLCN (Dutch Lipid Clinic Network) – criteria. Only one patient was a known FH-gene carrier before diagnosis of CAD. Only 20 patients from the cohort (13 probable/definite and 7 possible for FH) were analyzed using genetic testing. Five of them (25%) had pathogenic FH-variant and two of them were admitted to Department of Clinical Genetics for cascade screening. 142 (88%) of patients (94 with DLCNC score ≥6 and 48 with DLCNC score 5) had not been tested for genetic mutations of FH. None of the patients were diagnosed with FH based on clinical criteria before or after CAD.
Conclusions
FH is an underdiagnosed and undertreated condition. Automated screening tool in cardiac care could provide additional support for clinicians and reduce the inter-clinician variability in diagnostics, treatment and cascade screening of patients and family members potentially having FH. Further studies are needed to optimize the threshold values and exclusion criteria in the automated screening tool.

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AEP346

Sodium taurocholate cotransporting polypeptide (NTCP) is a new and promising target for treatment of hypercholesterolemia: A proof of concept from a randomized double-blind placebo-controlled phase I trial

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Bile acids (BAs) are synthesized by converting cholesterol in hepatocytes and recycling it via enterohepatic circulation. Most BAs are reabsorbed into hepatocytes, where they inhibit their own synthesis by activating FXR pathway. NTCP is a major transporter of BAs via absorption from portal blood into hepatocytes. Hepalatide is a 47aa synthetic peptide that specifically binds NTCP resulting in BA spillover of hepatocytes into the systemic circulation. In this way, BA synthesis is uncoupled from negative feedback and more cholesterol can be broken down, which presents a new strategy for lowering cholesterol. The current phase I trials included a single-dose escalating stage (NCT02612506) and a multiple-dose escalating stage (NCT03023787). In the single-dose trial, 45 healthy subjects were recruited into six cohorts with escalating doses of 0.525, 2.10, 4.20, 6.30, 8.40, and 10.50 mg. In each cohort, subjects were blindly randomized into the active and placebo groups at a 4:1 ratio. No SAE took place and there was no significant difference between the adverse events (AEs) in the hepalatide treatment and placebo cohorts. The concentration of BAs in plasma increased in a linear relationship with dosage. In the multiple-dose trial, 35 healthy subjects were recruited into three cohorts with escalating daily doses of 4.20, 6.30, and 8.40 mg for 7 days. In each cohort, subjects were blindly randomized into the active and placebo groups at a 4:1 ratio. No SAE were observed and no AE was more serious than grade I as defined using NCI CTCAE (Version 4.03). Increased concentration of plasma BAs was observed, which was normalized after drug withdrawal in all hepalatide treatment cohorts. The administration of hepalatide for 7 days reduced serum total cholesterol (TC) in a dose-dependent manner, resulting in a significantly lower TC in the 8.4 mg cohort at the end of the 7-day treatment than in the placebo cohort ($P=0.0029$). The LDL-c was decreased by an average of 20% in the 6.3 mg and 8.4 mg cohorts with a maximum decrease of 39% in one healthy subject. The reduction in LDL-c showed a significant difference between both the 6.3 mg and 8.4 mg cohorts and the placebo cohort.

In conclusion, administration of hepalatide increased peripheral BAs in a linear manner. Seven-day treatment with hepalatide reduced blood TC and LDL-c significantly. This is the first clinical trial to assess the concept of NTCP as a promising target for treatment of hypercholesterolemia.

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AEP347

Prevalence andassociated factors with sensitive neuropathy in a population of patients with diabetes

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Introduction
Sensitive neuropathy is a degenerative complication of diabetes, precipitated by chronic glycemic imbalance. It is estimated that it is present in 50% of diabetics, and that it requires treatment in 10 to 20% of cases.
This study aimedto assess the prevalence of sensitive neuropathy and to identify the factors associated with it in a population of patients with diabetes.
Patients and methods
This is a descriptive and analytical, prospective cross-sectional study, involving 100 diabetic patients. Screening for sensitive neuropathy (SN) was done by the Semmes-Weinstein monofilament test (10g). We studied the association of SN with: Smoking, diabetes duration, body mass index (BMI), glycemic control and the presence of diabetic retinopathy.
Results
The mean age was 54±12.9 years, The sex ratio was 0.78. Diabetes was type 2 in the majority of cases (78%). The average duration of diabetes was 13.62±6.29 years. 78% of the population has been unbalanced. The prevalence of sensitive neuropathy was 41%. In univariate analysis, the factors associated with NS were smoking ($P=10^{-3}$, OR [95% CI]=5.67 [2.2; 14.1], daration of diabetes >15 years ($P=10^{-3}$, OR [95% CI]=7.76 [3.1; 19.1]), diabetic retinopathy ($P=0.001$, OR [95% CI]=4, 6 [1.8; 11.6]) and glycemic imbalance ($P=0.015$, OR [95% CI]=4 [1.2 ; 13]. BMI was not an associated factor ($P=0.509$). In multivariate analysis, the factors associated with NS were the presence of diabetic retinopathy ($P=10$-3, OR [95% CI]=7.25 [2.5; 21]), smoking ($P=0.007$, OR [95% CI]=4.9 [1.5; 15.4]) and the duration of diabetes ($P=0.032$, OR [95% CI]=3.3 [0.8; 13.3]. The glycemic balance was not associated with NS ($P=0.09$, OR [95% CI]=3.3 [0.8; 13.3]).
Conclusion
Our results match those of the literature for most of the factors studied.

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AEP348

Assessment of renal insufficiency in the absence of albuminuria in patients with type 2 diabetes mellitus

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Introduction
Diabetic nephropathy is a clinical syndrome characterized by overt proteinuria and decreased renal function in the course of diabetes mellitus. The earliest symptom is the presence of albuminuria, but a decrease in glomerular filtration rate(GFR) has been observed in patients without albuminuria. In our study, it was aimed to investigate the presence and prevalence of nonalbuminuric diabetic kidney disease observed in patients with type 2 diabetes, and to determine the characteristics and prevalence of patient groups with this feature.
Material and methods
Normoalbuminuric ($n=138$), and albuminuric ($n=40$) patients records with T2DM over 40 years of age, followed by 2014–2018 in our clinic, with GFR < 60 ml/min/1.73 m^2 were examined retrospectively. Various demographic and diabetes-related clinical and laboratory features and risk factors of patients in the study group were recorded. These variables in the group of patients with normoalbuminuric were compared with albuminuric patients. During the comparison, nonparametric methods were used because the patient distribution wasn't normal. We want to share the data of the first 138 patients as a preliminary evaluation, since the study was not completed.
Results
In the study, 93 female and 45 male patients were found to be normoalbuminuric, 11 female and nine male patients were microalbuminuric, 12 female and eight male patients were macroalbuminuric. In the comparison between the groups, it was observed that normoalbuminuric patients were older than albuminuric patients, shorter diabetes duration, lower LDL and triglyceride levels, and HbA1C mean and arterial blood pressures were higher in albuminuric patients. Diabetes duration ($P=0.047$), HbA1C overall average ($P=0.048$), retinopathy ($P=0.017$) and macrovascular complications ($P=0.004$) compared to Mann-Whitney-U test were significantly different between the groups (Table 1). Microalbuminuric and macroalbuminuric patients were compared due to the difference between the albuminuric and non-albuminuric groups and no significant difference was found in the parameters ($P>0.05$).
Conclusion
These results emphasize the role of different variables in the development of diabetic nephropathy. Progress of renal dysfunction and albuminuria can be delayed if effective blood pressure control is achieved and blood lipids and HbA1C levels are kept within the treatment targets in normoalbuminuric patients.

Table 1 Statistics of normoalbuminuric and albuminuric patients.

	Normoalbüminuric($n=138$)	Albuminuric($n=40$)	*P*-value
Age(median)	68	67	0.176
Diabetes duration(-years)	15	20	0.047
BMI(m^2)(median)	31.15	30	0.488
HDL(mg/dl)(median)	42	42	0.811
LDL(mg/dl)(median)	115.1	117.5	0.473
Triglyceride(mg/dl)(median)	176	152	0.926
HbA1C overall average(%)(median)	7.59	8.5	0.048
Retinopathy(%)(median)	50	75	0.017
Macrovascular complications(%)(median)	73	50	0.04
SBP(mmHg)(median)	133	139	0.066
DBP(mmHg)(median)	80	81	0.523
Sex(Female)(%)	67.3	55	0.225

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AEP349

Rhinosinusal mucormycosis: A devastating infection in diabetes Mellitus

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Introduction
Mucormycosis is an unusual but serious fungal infection that most commonly affects people with diabetes mellitus. Treatment shoud be initiated urgently and associates antifungal treatment, surgical resection and control of risk factors. This infection is associated with high morbidity and mortality rates.
Case reports
We report three cases of rhinosinusal mucormycosis occuring occurring in one female and two males. The medium age of the patients was 57 years ranging from 52 to 65 years. Uncontroled diabetes was noted in the three cases. The first case was presented with a 4-day history of left facial oedema, exophtalmos and nasal obtsruction. The second and the third cases were presented with septic shock and an extensive acute nasal skin necrosis.

There was no history of fever, purulent discharge, paresthesia and foul odor. On examination, edema of the left hemiface as well as oculomotor paralysis and exophthalmos were noted for the first case, highly inflammatory nasal mucosa, purulent secretions, periortbital edema and black necrotic spot over the hemiface for the other cases. Facial CT scan examination showed signs of mucormycosis : maxillary, sphenoidal and ethmoidal sinusitis, with extension towards the soft tissues, bone erosion and orbit involvement in all the cases. Histological findings were consistent with mucormycosis.
Amphotericin B in combination with surgical debridement was used in the treatment of all the cases. A fatal outcome was noted in 2 cases.
Conclusion
Uncontrolled diabetes mellitus is considered to be the main predisposing factor for rhinosinusal mucormycosis. To prevent and reduce mortality rate of this acute disease, early diagnosis based on clinical findings and biopsy is recommended.

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AEP350

PHIGNA-DM2 study: Fatty liver and nonalcoholic steatohepatitis prevalence in type 2 diabetes in an andalusian cohort

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Introduction
Non-alcoholic fatty liver disease (NAFLD) is an underdiagnosed complication in Type 2 Diabetes (T2D). This condition can evolve into steatohepatitis (NASH) and more severe entities such as liver cirrhosis and hepatic failure, being currently the first cause for liver transplantation in our environment. In Andalusian T2D patients, the exact prevalence is still unknown. Our aim is to assess the prevalence of NAFLD/NASH in a cohort of these patients.
Material and methods
Descriptive prospective study, conducted at the Endocrinology Department of the Virgen del Rocio University Hospital between 10th May 2018 and 31st December 2019. After favourable evaluation from the local ethics committee, all T2D patients admitted to this department were offered enrolment, excluding those with pre-existing liver disease or alcohol abuse, as well as those below 18 years old. We used as screening tools the Hepatic Steatosis Index (HSI), Fibrosis-4 (FIB-4) and NAFLD Fibrosis Score (NFS), whose results were afterwards compared with transient elastography (FibroScan) obtained from the same patient. Quantitative variables were expressed as median [Interquartile range] while qualitative ones were recorded as n patients (percentage). This study was possible thanks to a supporting grant from Menarini Spain.
Results
Total sample $n=105$, 45 females (F) and 60 males (M), aged 60.0 years [53.5–68.5] (M 59 [54–68], F 63 [53–69]). BMI 34.21 Kg/m^2 [31.22–43.26] (M 33.76 [31.24–42.99], F 34.67 [30.54–43.26]). T2D duration: 9 years [4–16] (M 10.00 [5.25–19.00], F 9 [2.5–12.5]); HbA1c 7.30% [6.45–8.35] (M 7.40 [6.60–8.93], F 7.10 [6.20–7.80]). HSI: positive (>36) in $n=96$ (94.12%), median 46.55 [42.51–57.17]; FIB-4 risk of fibrosis: low risk (<1.3) $n=79$ (76.7%), moderate (2.66–1.30) $n=22$ (21.36%), very high (>2.67) $n=2$ (1.94%). NFS risk of fibrosis: low (<–1.455) $n=6$ (9.37%), moderate (–1.455 to 0.676) $n=42$ (65.63%), High/Very High (>0.676) $n=16$ (25.00%). Liver Elastography: No fibrosis/mild fibrosis F0-F1 (<7.5 kPa) $n=52$ (73.24%), Fibrosis F2 (7.5–9.5 kPa, moderate) $n=12$ (16.90%), Fibrosis F3 (9.5–14 kPa, severe) $n=4$ (5.63%), Cirrhosis F4 (> 14 kPa) $n=3$ (4.23%).
Conclusions
In our series, up to 26.76% of asymptomatic patients show moderate to severe hepatic fibrosis and are at risk of developing cirrhosis. FIB-4 seems to be more precise than NFS in estimating liver fibrosis degree. Our results, if confirmed in other populations, should made physicians aware of the importance of NASH in T2D and prompt the early screening and follow-up of this condition.

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AEP351

Evaluation of clinical factors predictive of diabetes remission after bariatric surgery

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Introduction
Bariatric surgery is an effective treatment in order to achieve an important weight loss and improvement of metabolic comorbidities. This study aimed to assess the clinical factors that can influenced on evolution of type 2 diabetes (T2D) and obesity patients after bariatric surgery.
Methods
We conducted a cohort study with a sample of patients with type 2 diabetes and class II obesity or above who underwent bariatric surgery at Hospital Universitario Puerta del Mar (Cadiz) from January 2005 to December 2016. We evaluated demographic variables, clinical and analytical parameters, anthropometric measurements and surgery complication rates. We analized the variables before and two years after surgery. The multivariate analysis includes the possible clinical factors that predict T2D remission two years after bariatric surgery.
Results
83 patients were included with a mean age of 44.13±10.38 years. Two years after surgery, the percentage of overweight lost was 63.43±18.59% and T2D was resolved in 79.5%. The body mass index range (RR: 1.886; $P=0.022$), T2D duration more than five years (RR: 0.022; $P=0.040$), baseline insulin treatment (RR: 0.001; $P=0.009$) and absence of macrovascular complications (RR: 34.667; $P=0.002$) were related with T2D remission. 15.6% of patients presented early complications and 20.5% developed late complications.
Conclusions
In our setting, bariatric surgery is an effective and safe technique for sustained weight loss in the mid-term, with a high rate of T2D's resolution. An absence of insulin treatment, higher baseline BMI, shorter T2DM duration and absence of macrovascular complications are factors predictive of diabetes remission after bariatric surgery.

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AEP352

The relationship between cardiovascular autonomic neuropathy and markers of oxidative stress in patients with type 2 diabetes mellitus

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Introduction
Cardiovascular autonomic neuropathy (CAN) is a significant risk factor for cardiovascular morbidity, mortality in patients with diabetes mellitus (DM). On the other hand, oxidative stress is one of the important factor of pathogenesis of diabetic complications. However, an association between CAN, cardiovascular autonomic reflex tests (CARTs), heart rate variability (HRV) and markers of oxidative stress in patients with DM was not fully investigated.
Objectives
The aim of this study was to investigate the relationship of CAN, CARTs, HRV and oxidative stress markers in patients with type 2 DM.
Materials and methods
We examined 15 patients with type 2 DM, six males and nine females (aged 60,1±1,61 years, duration of diabetes – 10,3 ±1,26 years, HbA1c – 9,1±0,69%) (data are presented everywhere as mean±s.e.m.). All patients were performed CARTs by Ewingand the followingmarkers of oxidative stress were measured in the plasma – superoxide dismutase, catalase, glutathione peroxidase, malondialdehyde. The diagnosis of CAN was confirmed in patients with 2 positive tests. The statistical analysis was performed using SPSS statistical package version 23.0 for Windows.
Results
CAN by 2 abnormal tests was diagnosed in 33,3% patients, and by 3 abnormal tests – in 66,7% patients. We found positive correlation between

levels of glutathione peroxidase and the 30:15 ratio, ($r=86.3$, $P<0.05$), and level ofcatalase and LF:HF ratio ($r=2.56$, $P<0.01$). Negative correlation was found between level of catalase and Valsalva ratio, ($r=-5.4$, $P<0.05$).
Conclusion
We found somerelationship between the presence of CANand markers of oxidative stress which could suggest the possible role of oxidative stress in the development of CAN in patients with type 2 DM.

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AEP353

Relationship between pregnancy induced hypertension in women with gestational diabetes mellitus and proinflamatory cytokines

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Justification and objectives
Gestational Diabetes Mellitus (GDM) is associated with an increased risk of Pregnancy-Induced Hypertension (PIH). Previous studies suggest a relationship between inflammatory markers and the development of PIH and obstetric and perinatal complications. The aim of the study was to establish the relationship between pro and anti-inflammatory cytokines and the development of PIH and the impact on obstetric and perinatal outcomes.
Material and methods
From an established prospective cohort of pregnant women with GDM, we studied 11 who developed PIH and 143 who remained normotensive; for reference values, we included 90 healthy non-diabetic normotensive pregnant women. Plasma levels of pro-inflammatory cytokineswere measured at 28–32 weeks of pregnancy, before the clinical onset of PIH. Baseline characteristics, metabolicparameters and obstetric and perinatal outcomes were analyzed.
Results
Higher levels of sFlt-1/PIGF ratio [4.92±2.72 vs 2.27±1.38, $P=0.009$] and lower levels of adiponectin [10.09±1.03 vs 12.88±2.74, $P=0.001$] were observed in pregnant women with GDM who developed PIH compared to normotensive women with GDM. Higher levels of resistin [7.20±3.02 vs 5.81±3.03, $P=0.001$] were observed in pregnant women with GDM compared to control group. We observed lower birth weight [2652.2±638.2 vs 3255±513.4 g, $P=0.011$], and higher prevalence of Small for Gestational Age (SGA) newborns [45.5 vs 8.4%, $P=0.003$] and Intrauterine Growth Retardation (IGR) [27.3 vs 4.2%, $P=0.018$] in pregnant women who developed PIH. Higher rate of hypoglycemia in newborn [27.3 vs 3.5%, $P=0.013$] were found in women with PIH compared to normotensive pregnant women.
Conclusions
We concluded that pregnant women with DMG who develop HIE have a characteristic proinflammatory profile, with significantly lower levels of adiponectin and a higher sFlt1/PlGF ratio. This group have a higher rate of adverse pregnancy and neonatal outcome compared to normotensive pregnant women: lower birth weight, a higher incidence of SGA and IGR, and higher prevalence of hypoglycemia in newborn.

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AEP354

The pattern of nerve involvement in type 1 diabetic patients with subclinical peripheral neuropathy

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The concept of a subclinical form of diabetic peripheral neuropathy (DPN) is well established. Although there has been considerable research of peripheral neuropathy in type 1 diabetes, still there is controversy regarding the pattern of nerve involvement in diabetic neuropathy. Detection of the pattern of nerve involvement can help to establish a protocol for screening of DPN in its subclinical stage.
Aim
The aim of this study was to describe the pattern of nerve involvement in type 1 diabetic patients with subclinical neuropathy using nerve conduction studies (NCS).
Materials and methods
65 patients with type 1 diabetes (DM1) and 34 controls without diabetes matched to the patient group were included. All patients and controls underwent a standard neurological examination (NSS and NDS (the variant used in Belarus) score) and bilateral NCS of the sensory and motor lower limb nerves using NeuroSoft machine. Interpretation of the results was based on the following normal reference ranges:n. Peroneus superficialis A>10 μV, v>45 m/s; n Suralis A>5 μV, v>45 m/s; n Peroneus profundus A>3 mV, v>40 m/s; n Tibialis A>3.5 mV, v>40 m/s.
Results
Clinically evident DPN was detected in 14 diabetic patients from 65 examined. The use of NCS allowed to identify the subclinical stage of polyneuropathy (abnormalities in at least two of the electrophysiological parameters) additionally in 35 patients who had no symptoms and clinical signs of DPN. Regarding abnormal NCS parameters in patients with subclinical diabetic neuropathy, amplitudes reduction for the *n*. Peroneus superficialis and n. Peroneus profundus predominated. Median of the amplitude for n. Peroneus superficialis in patients with subclinical DPN was 7.22 [5.25; 8.54] μV vs 12.4 [10.57; 16.2] μV in the controls, $P<0.001$; for n. Peroneus profundus 2.21 [1.68; 2.68] mV vs 3.15 [3.04; 3.42] mV, $P<0.001$. Significant differences in the amplitudes for *n*. Suralis and *n*. Tibialis has not been identified. Nerve conduction velocity (NCV) in patients with the subclinical DPN and the control groups was within the reference range. However, the medians of NCV for *n*. Suralis and *n*. Tibialis were significantly lower in the group of patients with neuropathy compared with the controls – 47.08 [44.35; 50.13] m/s vs 51.3 [47.6; 59.05] m/s, $P=0.025$ and 44.8 [42.15; 48.2] m/s vs 49.35 [48.30; 53.45] m/s, $P=0.004$, respectively.
Conclusion
In patients with type 1 diabetes with a subclinical stage of diabetic polyneuropathy the most frequent neurophysiological abnormality was reduced amplitudes (the axonal damage) for sensory and motor fibers of n. Peroneus.

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AEP355

Nursing networking for insulin pump therapy

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Objective
Diabetes mellitus is among the most common of chronic disorders with increasing prevalence worldwide, affecting 50000 citizens in Montenegro. The insulin pump is a medical device that works on the principle of continuous insulin injection, and is used in the control of diabetes in insulin dependent patients. The objective of this study was to highlight the role of nurse in education of the patients, implantation of insulin pump and nursing networking for insulin pump therapy in Montenegro.
Methods
The study enrolled all patients between 2016 and 2020 starting insulin pump therapy, 23 females and seven males. The indications were unsatisfactory glycoregulation, incipient nephropathy and pregnancy planning. Three patients discontinued insulin pump therapy during the further treatment.
Results
Patients were from different parts of Montenegro, central part 14 patients, southern 6 patients, and northern part 8 patients. The diabetes was diagnosed in patients between 2nd and 28th year. At the moment of the insulin pump therapy initiation the youngest patient was 16 year-old and the oldest patient was 56 year-old. Glycated hemoglobin before the insulin pump therapy initiation ranged between 5.2 and 12.4%, and after starting insulin pump therapy between 5.2 and 9.8%. Three female patients achieved pregnancyand healthy offspring, and also one male patient had healthy offspring. Seven female patients are in the process of planning pregnancy. The most common diabetes complications was diabetic nephropathy and neuropathy, and the most common comorbidity was primary hypothyroidism in chronic autoimmune thyroiditis. Finally, the study results showed that glycoregulation was significantly better in patients with continuous nurses support than those with standard care.

Conclusions
The nurse has a very important role in the insulin pump implantation team in education of the patients for using insulin pump and better understanding its technical characteristics, as well as knowing how to calculate carbohydrate units for the each meal. Improving awareness of insulin pump therapy as a mode of insulindelivery and creating confidence in caring for patients with insulin pump is essential in improving their glycoregulation.

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Effect of lipid metabolism of mothers with type 1 diabetes and obesity on clinical and laboratory parameters of their newborns

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Background and objective
According to recent studies, adipose tissue produces important biological factors (adipokines include leptin, adiponectin, etc.) for hormonal, lipid and glucose metabolism, insulin resistance, endothelial dysfunction and atherosclerosis development. The study of this factors and it's correlation with maternal lipid metabolism and neonatal anthropometric characteristics would be of great interest.
This study aims to analyze lipid metabolism features in women with type 1 diabetes T1D and/or obesity and it's correlation with newborns' hormonal and anthropometric parameters.
Methods
A prospective observational study was performed in RSPC «Mother and child» in 2018–2019. 89 full-term neonates from mothers with DT 1 and excess body weight/obesity were divided into 4 groups: Gr1 – from mothers with T1D and BMI<25.0 kg/m^2 (n=25); Gr2 – from mothers with T1D and BMI≥25.0 kg/m^2 (n=21); Gr3 – from mothers with BMI≥25.0 kg/m^2 (n=18); control group (GrC) – from mothers without diabetes and healthy BMI (n=25). Neonates' BMI was 13.86 [13.14; 14.98], 14.36 [13.42; 14.77], 13.05 [12.57; 13.27], 12.00 [11.70; 12.04] kg/m^2 ($P_{1\text{-}C}$=0.002, $P_{2\text{-}C}$=0.002, $P_{3\text{-}C}$=0.007, $P_{1\text{–}3}$=0.016, $P_{2\text{–}3}$=0.004), Z-scoreBody weigh – 0.90 [0.45; 3.10], 2.15 [1.18; 2.24], 0.60 [0.11; 1.10], –0.47 [–0.57; –0.16] ($P_{1\text{-}C}$=0.002; $P_{2\text{-}C}$=0.002; $P_{3\text{-}C}$=0.012; $P_{2\text{–}3}$=0.001). Physical development indicators for newborns were assessed using Intergrowth-21st. Statistica 10.0 was used for statistical analysis.
Results
Mothers' serum cholesterol level during first stage of labor was 9.1 [7.9; 10.9], 9.8 [7.6; 10.4], 7.5 [6.1; 7.8], 9.4 [9.2; 10.0] mmol/l ($P_{1\text{–}3}$=0.006, $P_{2\text{–}3}$=0.018); TGc – 3.8 [2.6; 4.9], 3.8 [2.2; 5.1], 2.7[2.0; 3.3], 2.7 [2.5; 4.1] mmol/l ($P_{2\text{–}3}$=0.018); LDL-P – 4.4 [4.1; 5.9], 4.8 [3.9; 5.4], 3.7 [3.2; 4.2], 4.9 [4.4; 5.2] mmol/l ($P_{1\text{–}3}$=0.007, $P_{2\text{–}3}$=0.018). Leptin levels in the 1st day of life in Gr1, Gr2, Gr3– 5.10 [3.18; 28.06], 35.78 [6.43; 47.47], 5.46 [2.13; 9.16] ng/ml ($P_{2\text{–}3}$=0.043). Gr1, Gr2, Gr3, GrC cord blood leptin levels – 5.3 [4.0; 23.3], 7.9 [4.2; 49.5], 17.4 [7.3; 20.4] ng/ml. We found out a positive correlation between mothers' TGc, HDLP and neonates' cord blood leptin levels (r=0.512, r=0.658); TGc, LDL-P and leptin levels in the 1st day of life (r=0.525, r=0.523). We revealed a positive correlation (P<0.05) between newborns' hormonal and anthropometric parameters: leptin levels in the 1st day of life and body weight (r=0.594), body weight z-score (r=0.634).
Conclusions
Maternal lipid metabolism has great impact on their newborns' hormonal and anthropometric parameters. Further study of metabolic disorders in babies from mothers with T1D and obesity can help to improve medical care quality in the neonatal period.

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AEP357

Different steroidogenesis in patients with alzheimer's disease and Type 2 diabetes mellitus

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Alzheimer's disease (AD) is a neurodegenerative diseasethat is manifested by a progressive loss of cognitive and behavioral function. In previous studies, we have constructed a predictive model for the classification of AD patients based on levels of circulating steroids and their polar conjugates.
Both AD and Type 2 diabetes mellitus(T2DM) are well known to affect the levels of some steroid hormones, however, in the opposite direction, and in a gender-dependent manner. The aim of this study was to determine whether AD patients can be identified in the group of T2DM patients based on circulating steroids and their polar conjugates.
Methods
We evaluated the spectrum of steroid hormones in 86 patients with T2DM. The group consisted of 54 women (median age 71.2 years) and 32 men (median age 69.6 years), seven women and seven men had both AD and T2DM, the remaining 47 women and 25 men had only T2DM. To evaluate the balance between the steroids in reversible metabolic steps or activities of steroidogenic enzymes, we used product to precursor ratios. The data were processed by GLM ANOVA and multidimensional regression using O2PLS method (Statgraphics 18 × 64, SIMCA v 12.0).
Results
T2DM patients with AD generally exhibited lower adrenal steroidogenesis compared to T2DM patients without AD. Furthermore, there was decreased steroid sulfotransferase (SULT2A1) and 5α-Reductases (SRD5A) activities in the combined group of T2DM and AD but increased aldoketoreductases of subfamily 1C (AKR1C1) activity in both genders.
Conclusion
By using our O2PLS model, it is possible to distinguish between the group of patients with T2DM + AD and the group of only T2DM. The predictivity of the OPLS model for men is high: sensitivity = 0.875 (0.529, 0.978) and specificity = 1 (0.857, 1)as well as for women: sensitivity = 1 (0.646, 1) and specificity = 1 (0.917, 1).
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AEP358

The trio of severe hypertriglyceridemia, acute pancreatitis and diabetic ketoacidosisin a young subject not known before with diabetes. A case report

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Introduction
The trio of severe hypertriglyceridemia, acute pancreatitis and diabetic ketoacidosis (DKA) is a rare occurrence. Previous cases have presented DKA as the initial factor, contributing to subsequent hypertriglyceridemia and pancreatitis. Moderate hypertriglyceridemia is commonly observed in DKA but severe hypertriglyceridemia is very rarely reported.
Case report
We report a case, male 29 years old, diagnosed with hypertriglyceridemia 3 years ago. There was no family history for diabetes mellitus (DM) but his father was being treated for hypertriglyceridemia. Our patient referred that the last 3 years of his life were very stressful and with an unhealthy lifestyle. He did not use alcohol and was not a smoker. He was treated with fibrates during first year but he has stopped them himself. He was presented at emergency unit with 24-hour history of upper abdominal pain, nausea, vomitus, polyuria, fatigue and high temperature. Conscious, tachycardic, normotensive, febrile, overweight. On abdominal palpation, he felt epigastrium pain. Laboratory examinations: Severe hypertriglyceridemia (>5000 mg/dl), hyperglycemia, elevated amylase and lipase. Leukocytosis with high neutrophils. Elevated C-reactive protein. Electrolytes normal level. Urine analyses: ketonuria, glucosuria and infection. Arterial blood gases: mild metabolic acidosis. HbA1c11.9%, C-peptide normal, all autoimmune markers for DMT1 resulted negative. Abdominal ultrasound showed hepatosteatosis grade 2 and was suggestive of acute pancreatitis. Firstly, he was hospitalized in intensive unit care where he was treated with insulin, liquids I/v, antibiotics and fibrates without oral food. After 48 hours he got out of diabetic ketoacidosis but upper abdominal pain kept going. An abdominal CT scan showed images of acute pancreatitis. In consultation with gastrohepatologist, he was treated with non-steroid anti-inflammatory drugs associated with inhibitors of proton-pump without oral food. After 2 days he was without upper abdominal pain. He transferred to Endocrinology Department where he started

oral food associated with pancreatic enzymes. After ten days he discharged in good condition under treatment with fibrates, omega oils and statin, insulin for hyperglycemia and pancreatic enzymes. 2 weeks later, he stopped insulin because of normoglycemia and after 1 month, he had normal lipid level in blood under treatment. He is following a healthy life style.
Conclusion
Untreated a pre-existing lipid disorder especially in subject with an unhealthy life-style and a stressful life can lead to the rare trio of severe hypertriglyceridemia, acute pancreatitis and diabetic ketoacidosis, a life-threatening situation. Every medical physician must be aware of this situation to do the early correct intervention to prevent it.

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Case of type 1 diabetes development after programmed cell death-1 inhibitor immunotherapy

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Programmed cell death-1 (PD-1) receptor inhibitor is an immune check point blockade for anticancer treatment and is currently used for various malignancies such as melanoma, non-small cell lung cancer, and so on. However, an immune check point blockade is associated with a risk for immune related adverse events. Among these events, Type 1 diabetes is rare. We present a case of a 52-year-old man, with no previously diabetic history, who developed diabetic ketoacidosis (DKA) after 10 doses of nivolumab for non-small cell lung cancer. One week after the 10th nivolumab therapy, he visited the emergency room because he had severe nausea and vomiting and was diagnosed DKA. He had a glycemia of 616 mg/dl, and arterial blood gas values showed a pH of 6.982 and very low bicarbonate. After continuous IV insulin and hydration, glucose level and acidosis was normalized. Further testing showed C peptide level was 0.26 ng/ml, insulin antibody was 7.18% (normal range ≤7%) and glutamic acid decarboxylase antibody was 0.13 U/ml (normal range 0–1.00 U/ml). Basal bolus multiple daily injections were started for glycaemic control. In addition, thyroid function was changed from thyrotoxicosis to overt hypothyroidism suggesting he had thyroiditis. One month later, he restarted nivolumab treatment with multiple insulin injections without any additional adverse events.
Physicians are becoming more aware of immune adverse event because the treatment using immune check point is increasing. Therefore, blood glucose monitoring during PD-1 inhibitor is necessary to avoid diabetic ketoacidosis

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Arare case of caucasian patient with insulin autoimmune syndrome induced by a-lipoic acid

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Introduction
Insulin autoimmune syndrome (IAS) is characterized by spontaneous hypoglycemia caused by insulin autoantibodies (IA) in the absence of exogenous insulin administration. The occurrence of IAS may be influenced by a genetic predisposition determined by HLA class II. IAS is frequently reported in Japanese and Koreans due to their genetic predisposition (HLA-DRB1*0406) rather than in the Caucasians. Some drugs containing sulfhydryl compounds are known to initiate the onset of IAS. A-lipoic acid (ALA) contains two sulfur atoms and can promote insulin S-S bounding dissociation and expose insulin to the antigen presenting cells. T cells of predisposed patients are stimulated, resulting in IA formation.
Case description
A 52-year-old female with medical history of oral medical supplements consumption, containing ALA, was admitted at the emergency Department with severe hypoglycemia accompanied by neuroglycopenic and adrenergic symptoms. Intravenous dextrose solutions along with many short mixed meals were administrated. After the exclusion of adrenal insufficiency and hypothyroidism, a 72-hour fasting test was attempted, but was ended 3 hours later because the patient experienced palpitation and sweating with low blood glucose level (39 mg/dl). Serum insulin and c-peptide levels were high (27.7 μI U/ml and 2.7 ng/ml respectively). Pancreatic Magnetic tomography and endoscopic ultrasonography did not prove the existence of an insulinoma while IA levels were very high (101 U/ml). The excessive consumption of medical supplements, containing ALA [which improve glucose metabolism], the absence of other clinical signs and the high IA levels established the diagnosis of IAS. ALA supplementations were discontinued and diazoxide was initiated. Glucose levels were increased and after three months of treatment, the patient was recovered completely. IA were decreased, but they have not been normalized yet. Diazoxide treatment was gradually decreased and discontinued. Her HLA genotype analysis has not been completed yet.
Conclusion
IAS should be considered in patients with sudden episodes of hypoglycemia, when the imaging investigation was unremarkable and medications containing sulfhydryl compounds, such as ALA were consumed.
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AEP361

Autoimmune causes of hypoglycemia

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Background
Identifying the etiology of hypoglycemia in a non-diabetic patient is a significant challenge. Hyperinsulinemic hypoglycemia can lead to pancreatectomy in patients with no evident organic disease. Insulin autoimmune syndrome (IAS) or Hirata diseaseand Type B insulin resistance syndrome are the two typesof autoimmune hypoglycemia, with a low worldwide prevalence.
Objective
We report two real-lifecases that illustrate each of them.
Results
The first case depicts a 69-year-old woman who had frequent episodes of symptomatic hypoglycemia, which happened to occur three hours after the intake of food. Amonth earlier, she had received a 7-day treatment with amoxicillin. Besides, she had a daughter with type 1 diabetes, celiac disease and autoimmune subclinical hypothyroidism. She underwent a prolonged fast test in which no clinical or analytical hypoglycemia were found. Nevertheless, severe hyperinsulinemia was detected, even though it wasnot correlated with the levels of serum glucose, C peptide and proinsulin, which showed normal values. Insulin autoantibodies (IAA) were positive with a 76.8% fixation (RV<8.2%). Moreover, there was no pathological finding within HbA1, nor the adrenal, thyroid and somatotroph axis. In addition, sulfonylureas were not detected in urine. Afterwards, the oral glucose tolerance test showed initial hyperglycemia (insulin bound by IAA becomes ineffective), followed by hypoglycemia due to the release of the insulin-IAA complexes. A diet low in simple carbohydrates and frequent intake of small meals encouraged a successful clinical evolution of the IAS. On the other hand, the second patient was a three-year-old girl, with neonatal diagnosis of DiGeorge syndrome, who had suffered various episodes of symptomatic hypoglycemia with no obvious cause. In this case, the patient showed a remarkable acanthosis nigricans and high glucose variability. Severe hyperinsulinemia and very low serum glucose levels were simultaneously found, with normal C peptide. Nonetheless, anti-insulin antibodies and the exhaustive study for hyperinsulinism were negative. Frequent hospitalizations in relation to severe respiratory infections ended-up with a combined therapy of high-dose corticotherapy and gammaglobulins. From that moment on, serum insulin levels progressively decreased until normalisation and hypoglycemia eventually disappeared. Pending the results of the anti-insulin receptor antibodies (sent to an international laboratory) to confirm the diagnosis, the clinical picturecould be considered asthe type B insulin resistance syndrome.

Conclusions
Autoimmunity related to insulin or to insulin receptor should be ruled out in order to reach the aforementioned uncommon diagnoses, ensuring a correct clinical management and avoiding an unnecessary and non-effective pancreatic surgery.

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Cardiovascular manifestation of alkaptonuria

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Case History
A 64-year-old gentleman presented with progressive exertional breathlessness since 1 year. He had started noticing pigmentation in the eyes 2 years back, and gave a history of passing black coloured urine since childhood. He had never consulted a medical professional for the same. Examination revealed hyperpigmentation of both ears and conjunctivae, and an ejection systolic murmur (Grade V) at the aortic area, which radiated to both his carotids. A sample of his urine revealed the colour of his urine to be cola-coloured. Echocardiography confirmed valvular aortic stenosis with the pressure gradient across the aortic valve being 72 mm Hg, and the valve area being 0.8 cm^2. The gas chromatography-mass spectrometry analysis of his urine revealed that urinary levels of homogentisic acid were elevated, thus confirming the diagnosis of alkaptonuria. He refused surgery, hence, after a discussion between the patient, the treating cardiologist, and the cardiothoracic surgeon, a transcatheter aortic valve replacement (TAVR) was done by his cardiologist. Alkaptonuria, one of the first disorders in humans found to conform with the principles of Mendelian recessive inheritance[1], is a rare hereditary disorder in which deficiency of homogentisate 1,2 dioxygenase (HGD) (the enzyme predominantly produced by hepatocytes in the liver and within the kidney, and is responsible for the breakdown of HGA; an intermediate in the tyrosine degradation pathway) leads to urinary excretion of homogentisic acid in large amounts, which darkens on standing[2]. Accumulation of oxidized homogentisic acid pigment in connective tissue (ochronosis) also occurs, namely in the sclerae of the eye, as well as the concha of the ear[3]. The disease may be picked in the patients when they are young owing to the peculiar colour of their urine, but may often be ignored until their latter years. Patients usually present with degenerative arthritis in the middle age. Degenerative cardiac disease, especially aortic stenosis as in this case, may also occur and is an important clinical problem in older patients[4].
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The quantitative relationship between Autonomous cortisol secretion, Dysglycemia and the Metabolic syndrome

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Objective
Autonomous cortisol secretion (ACS) is the most common endocrine abnormality in the evaluation of adrenal incidentalomas. The categorization of ACS is derived from a 1 mg dexamethasone suppression test (DST). Impaired DST is associated with several metabolic derangements. In this study we assess the correlation between post-DST cortisol level, analyzed as a continuous parameter, and indices of glycemic metabolism.
Study design
We prospectively collected data of 1976 patients evaluated for adrenal incidentalomas in a large tertiary medical center between December 1st, 2017 and August 31st, 2019. 73 patients completed the evaluation process. Post-DST cortisol levels were analyzed for correlation with various metabolic parameters, including fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) among the general cohort and for subgroups stratified by the number of metabolic syndrome (MS) criteria.
Results
Post-DST cortisol demonstrated a linear correlation with FPG and HbA1c across its entire cortisol range ($R=0.51$ and 0.41, respectively, $P\leq0.01$). The correlation between post-DST cortisol and FPG was strengthened with increased number of metabolic syndrome criteria. Patients with 4 MS criteria show a stronger correlation ($R=0.92$) compared to patients with only a single criterion ($R=0.509$). Furthermore, mean post-DST cortisol levels increased as the number of MS criteria accumulated.
Conclusion
Post-DST cortisol should be viewed as a continuous parameter in risk stratification algorithms for development of the MS and particularly dysglycemia.

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***In vitro* and *in vivo* insulinotropic actions of magainin-AM1 on pancreatic beta cells and high fat fed mice**

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Aim
Insulin-releasing effects and potential anti-diabetic actions of peptides isolated from the skin secretion of the African clawed frog, *Xenopus amieti* has been reported. However, peptides such as magainin-AM1 has not been previously studied for its ability to stimulate insulin secretion or promote glucose uptake. This study investigated insulin releasing effects as well as possible underlying mechanisms.
Methods
Acute and chronic actions of magainin-AM1 were investigated using clonal pancreatic beta cells, BRIN-BD11, in buffers containing increasing glucose concentrations, magainin-AM1 alone (0–3 µM) or magainin-AM1 (1 µM) with modulators of insulin secretion. Insulin concentrations were measured by ELISA. Cytotoxicity and cell viability were examined in peptide-treated cells. Membrane potential and intracellular calcium concentrations were measured using Flexstation scanning fluorimeter. Glucose tolerance and insulin secretion were monitored in peptide-treated diabetic mice.
Results
Magainin-AM1 acutely stimulated insulin release from BRIN-BD11 cells in a concentration-dependent manner (1.4–1.6-fold, 100 nM–3 µM, $P<0.001$–0.05). The stimulatory effects of magainin-AM1 reduced in the presence of diazoxide (28%, $P<0.01$), verapamil 31%, $P<0.01$), calcium-free buffer (31%, $P<0.001$) and increased in incubations containing KCl (1.1-fold, $P<0.05$). Pre-treatment of cells with magainin-AM1 increased secretory responses to KCl (1.3-fold, $P<0.05$) but had no effect on responses to other secretagogues. These actions are not associated with reduced cell viability and cytotoxicity. Membrane potential and intracellular calcium concentration were increased by 1.9-fold ($P<0.01$) and 1.5-fold ($P<0.001$) in peptide-treated cells. Reduced blood glucose 24%, $P<0.05$) and enhanced insulin secretion (1.6-fold, $P<0.05$) were observed in peptide-treated mice.
Conclusions
These results suggest that the anti-diabetic properties of magainin-AM1 may involve the K_{ATP}-dependent pathway.

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The acute effects of short-term insulin therapy on the secretory ability of beta cells in patients with diabetes mellitus type 2, after the secondary failure of the oral therapy

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Introduction
Secondary failure (SF) to treatment with oral therapy is defined as the absence of a favorable reaction to the oral therapy which was effective in the previous course of the treatment. The aim of the work was to investigate the acute effects of the short-term insulin therapy on the secretory ability of endocrine pancreatic beta cells and the insulin resistance. Materials and Methods: 98 patients with diabetes mellitus type 2 (DM T2) and confirmed the SF to the oral therapy were selected for the study. These patients were divided into two different groups based on their body weight, and each group received a different insulin treatment regimens. The patients with a normal body mass (group A) were treated with a mono-insulin intensive conventional therapy (so called Basal-bolus regimen), while the group B patients (the group with an increased body mass) were treated with a combined insulin therapy (basal insulin plus metformin) in the duration of three months. All involved patients were tested prior to the insulin therapy and then three months after its startfor the factors of glycoregulation (glycated hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), 2h postprandial glucose (2h-PPG) and selfmonitoring of blood glucose (SMBG), and the homeostatic models for the estimation of values forthe insulin secretion and resistance (HOMA-β% and HOMA-IR) were calculated from the pairs of fasting glycemia and insulinemia. Main results: Results of the study show the improvement in glycoregulation, a decrease in insulin resistance (IR) and improvement in the endogenous pancreatic capacity for the both tested groups, when compared to the period prior to the insulin therapy started. Group A: FPG (9.5 vs 6.1, $P<0.001$), 2h-PPG (11.6 vs 6.9, $P<0.001$), HbA1c (9.0 vs 6.7, $P<0.001$), HOMA-β% (39.03 vs 83.42, $P<0.001$), HOMA-IR (4.87 vs 2.45, $P<0.001$). Group B: FPG (9.4 vs 6.3, $P<0.001$), 2h-PPG (11.6 vs 6.9, $P<0.001$), HbA1c (9.0 vs 6.7, $P<0.001$), HOMA-β% (54.8 vs 96.92, $P<0.001$), HOMA-IR (7.27 vs 3.38, $P<0.001$). Conclusion: The short-term insulin therapy, including normal-weight and overweight patients with DM T2 results in an improvement of glycoregulation, decrease in insulin resistance and recovery of secretory ability of beta cells of endocrine pancreas. Key words: secondary failure, diabetes mellitus type 2, HOMA-β%, HOMA-IR.

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Clinical pharmacology of insulin aspart: Hyperinsulinemic euglycemic clamp study of the biosimilar product

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Introduction
Rapid-acting insulins is widely used in the treatment of either type 1 diabetes mellitus, or type 2 diabetes mellitus. A mealtime injection of rapid-acting insulin, such as insulin aspart, allow the diabetic patients to control the levels of post-prandial glucose. The clinical development plan of the insulin biosimilarsusually contains pharmacology studies to evaluate pharmacokinetics (PK), pharmacodynamics (PD) and clinical safety of the investigational products.
To demonstrate Insulin Aspart, solution for intravenous and subcutaneous administration, 100 U/ml (GEROPHARM, Russia) and NovoRapid Penfill, solution for intravenous and subcutaneous administration, 100 U/ml (Novo Nordisk, Denmark) have comparable PK/PD profiles hyperinsulinemic euglycemic clamp (HEC) in healthy volunteers has been performed.
Methods
26 healthy male Caucasian volunteers aged between 18 to 50 years were subjected in a randomized, double-blind, crossover study of the comparative pharmacokinetics of the two different formulations of insulin aspart: Insulin Aspart, GEROPHARM (test drug, T) and NovoRapid Penfill, Novo Nordisk (reference drug, R). Subjects who met the inclusion/non-inclusion criteria underwent the procedure of HECfollowing the subcutaneous injections either T (0.3 IU/kg) or R (0.3 IU/kg) in the abdomen region. After the performed injections of insulin aspart, the levels of plasma glucose were monitored every 5 minutes for 8 hours. The adjustment of the glucose infusion rates was based on the blood glucose measurements. This data was used to evaluate the PD profiles of investigational drugs. Regular blood samplingwas performed during the study. The insulin concentrations in the blood samples of the subjects were determined using avalidated ELISA method. The results of the analytic procedures were used to calculate the PK parameters of insulin aspart and fit the concentration-time curves. The clinical study was approved by The Ministry of Health of the Russian Federation, as well as by the independent local ethical committees (NCT04184466).
Results
The confidence intervals for the ratio of the geometric mean of Insulin Aspart (GEROPHARM) for C_{ins} and AUC_{ins-t} were 110.51–124.02% and 102.12–110.24% respectively; for GIR_{max} and AUC_{GIR0-t} – 94.35–117.53% and 91.09–113.84%. Both PK and PD parameters were well within 80–125% limits for establishing comparability between two formulations of insulin aspart.
Conclusions
Our data demonstrated, thatInsulin Aspart (GEROPHARM) and NovoRapid Penfill (NovoNordisk) have comparable PK and PD profiles in healthy subjects in HEC paradigm. Thus, in this clinical trial the high level of similarity of R and T formulations of insulin aspart was experimentally confirmed.

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Does short term intensive insulin therapy in newly diagnosed type 2 diabetes mellitus delay eventual insulin dependence?

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In patients with type 2 diabetes mellitus (T2DM), dysfunction of β-cellsstarts years before the diagnosis of T2DM and rapidly worsens after overt hyperglycemia. Use of short-term intensive insulin therapy (STIIT) at the time of diagnosis of overt hyperglycemia has shown clinical recovery of β-cells for up to 2 years. A systematic literature review of studies looking for the effect of STIIT, used within two years of diagnosis of T2DM, on the duration from relapse of hyperglycemiato eventual insulin dependence is presented in this abstract. The key phrases ‘type 2 diabetes mellitus’, ‘short-term insulin therapy’, ‘β-cellfailure’, and ‘permanent insulin dependence’ were used to search English literature. For simplicity the duration of diabetes in these studies was divided into three periods: Period 1. Diagnosis of T2DM to end of STIIT which includes total weeks of STIIT, Period 2. End of STIIT until relapse of hyperglycemia i.e. total glycemic remission period, and Period 3. Relapse of hyperglycemia to permanent dependence on insulin therapy. Studies were excluded if all of their participants had diagnosis of T2DM for more than 2 years at the time of inclusion, i.e., if period 1 was more than 2 years. Six clinical trials involving STIIT were identified (Period 2). No studies that examined the clinical course of T2DM in their patients beyond the relapse of hyperglycemia (Period 3) were identified. This literature review identified a lack of data about this important clinical question- do ‘recovered’ β-cells from STIIT exhibit a better response to non-insulin therapies after the end of period 2 and, hence, delay the secondary β-cell failure in period 3?There is a need to conduct studies with longer follow up to characterize the differences in the disease course between patients treated with STIIT and patients treated with non-insulin therapies. This can help us understand the scope of STIIT beyond the initial functional remission of β-cells.

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Nurse education in diabetes and endocrinology – important part of the improvement of care provided to people with diabetes and other endocrine disorders

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Background and aims
Diabetes (DM) is a huge global health emergency of the 21st century. Around 463 million adults haveDM. Every 2-nd adult with DM is undiagnosed. Over 374 million people have impaired glucose tolerance, their risk of developing DM is very high. According to Diabetes Atlas-2019 DM national prevalence for Georgia is 7.1%. Increasing prevalence of DM/other endocrine disorders, specific health needs ofthese populations, increasing load on healthcare require more active nurse involvement inprovision of DM/endocrine care. Though globally nurses role in DM prevention/care is important, there are no trained diabetes or endocrine nurses in Georgia, who receive properknowledge on DM/other endocrine problemswhile studying at the collage.
Methods
Under the initiative of the Association of Professional Development of Georgian Nurses and Nurse Assistants Post Diploma Training of nurses was initiated in 2015. A Memorandum of Understanding and Support was signed with Georgian Union of Diabetes and Endocrine Associations, and DM was included as one of the 10 Modules of the Training Program. Diabetes Module for nurses started in 2016; it is a 2-day, 10 hour training; screening, diagnosis, management and prevention of DM/ its complication are discussed. Contracts were signed with several in-hospital and out-hospital medical facilities. Besides, together with Georgian Association of Medical Education and Evidence-Based Medicine a Summer School on Diabetes/Endocrinology for Nurses is functioning since 2016.
Results
Trainings were carried out in 5 cities; over 300 cardiology, surgery, endocrinology, obstetrics/gynecology, laboratory nurses were trained. During initial testing 3–4 out of 5 replies were wrong. Final testing showed significant improvement in knowledge. Manual for Nurses was prepared/printed. Medical facilities requested continuation of trainings continue; Course in Endocrinology for nurses will start in 2020.
Conclusion
Diabetes as one of non-communicable diseases (NCDs) has allocated a large proportion of cost, time and human resources of health systems. If other endocrinopathies are added the burden may ruin almost any health system. Nurses are health care providers who should be actively involved in prevention and early detection of DM/its complications and other endocrine disorders. After adoption of UNO Political Declaration and WHO Resolutions on NCDs, Governments are paying more attention to these conditions. The role of nurseshas started to change. We need not only totrain nurse-podiatrists, educators, diabetes/endocrine nurses, but to train all nurses in DM/endocrinology. There is an increased need for establishing new nurse specialties, such as nurse-practitioners/nurse-specialists to provide high-quality diabetes/endocrine care.

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Insulin regulated aminopeptidase (IRAP) inhibition affects glucose metabolism in obese pre-diabetic Zucker rats

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Skeletal muscle and adipose tissue has been identified as an endocrine organ and their metabolism exerts an impact on whole-body metabolism. Endocrine functions attributed to adipokines and myokines are involved in body weight regulation and insulin sensitivity. Obesity is associated with dys-regulation of adipose tissue and skeletal muscle metabolism and is accompanied with insulin resistance. Our study investigates the effect of insulin regulated aminopeptidase (IRAP) inhibition on the regulatory mechanisms of metabolism of subcutaneous and visceral adipose tissue and skeletal muscle in the fully developed stage of obesity and insulin resistance in Zucker rats. The obese Zucker rats, the genetic model of obesity, pre-diabetes and metabolic syndrome, were administered with an IRAP inhibitor – HFI-419 (MerckMillipore, Germany) at a dose of 29 µg/100 g/day by osmotic minipumps. Glucose utilization was monitored by the intraperitoneal glucose tolerance test (ipGTT) and measured in the blood of the rat tail. In the tissues of interest, gene expression was determined by real-time quantitative PCR and protein expression was measured by Western blot. IRAP inhibition improved glucose utilization and significantly decreased the area under the curve for the glucose level during ipGTT. In visceral adipose tissue, we observed significantly up-regulated protein expression of Akt protein and AS160 (Akt substrate 160 kDa) protein phosphorylation in obese rats treated with HFI-419 in comparison with obese controls, indicating stimulation of the insulin receptorsignalling pathway. In subcutaneous fat depot, administration of HFI-419 significantly reduced expression of glucose transporter GLUT1. In skeletal muscle, significantly increased expression of sirtuin 1 (SIRT1) and superoxide dismutase1 and 2 (SOD1, SOD2), was found. Our results showed an improvement in glucose utilization during theglucose tolerance testafter administration of an IRAP inhibitor in insulin resistant obese Zucker rats. In the tissues studied, we revealed different molecular mechanisms leading to improvement of insulinsensitivity of these tissues. We conclude that thepositive metabolic effect of the IRAP inhibitor observed in obese rats is the improvement of glucose transport into adipocytes and theregulation of redox balance inskeletal muscle. The study was supported by grants VEGA 2/0174/17 and APVV-15-0229 grants.

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Relationship of blood dopamine and leptin with anthropometric data in childhood obesity

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Background
Some of neurohormonal peptides, such as dopamine and leptin, get involved in modulationof food ingestion, eating behaviorand obesity.
Study aim was to detect associations blood dopamine, leptin and anthropometric indexes to predict the probability of obesity in children.
Material and methods
223 children (11–17.9 y.; II – V Tanner stages) with BMI ≥2 SDS and BMI=±1 SDS (normal weight (NW) were included into retrospective cross-sectional study. We use anthropometric data (weight, height, BMI, SDS BMI); blood dopamine (DA) and leptin (L) concentrations results (enzyme-linked immunosorbent assay method). Children were split up into three groups: NW (n=30); alimentary obesity (AO, SDS BMI ≥2 &≤4; n=86), extreme obesity (EO, SDS BMI>4; n=107) andalso into gender (girls/boys; n=111/112) and pubertal subgroups (early (EP)/late puberty (LP); n=71/152). Statistical analysis was performed using non-parametrical indexes, Spearman's correlations and binary logistic regression (P<0.05).
Results
DA levels were increased in EO children (30.00 (7.60–97.50) pg/ml) relatively NW (6,28 (4,57–26,54) pg/ml; P=0,003) and AO peers (10,44 (4,80–46,88) pg/ml; P=0,01). Only boys had similar pattern of blood DA differences: 31.88 (9,69–93,75) pg/ml in EO group, compared to NW – 6,46 (3,73–26,54) pg/ml; P=0,008) and AOpeers (7,83 (4,47–13,04) pg/ml; P=0,001). Girls did not have DA differences (P>0.05). DA levels had weak positive correlations with BMI (r=0.4; P<0,001) and BMI SDS (r=0.4; P=0.002)in the both gender LP patients. L concentrations gradual raised from NW group (4.77 (2.43–11.06); P_{NW-AO}<0.001); through AO (22.65 (12.60–35.86); P_{AO-EO}=0.02) to EO peers (31.29 (18.67–50.70) ng/ml; P_{EO-NW}<0.001). Girls had the same

pattern of raised Lconcentrations ($P \leq 0.001$). L levels had mild correlation with BMI ($r=0.6$; $P<0.001$) and BMI SDS ($r=0.7$; $P<0.001$) in EP childrenrelatively to LP peers ($r=0.3$; $P=0,01$ and $r=0.4$; $P=0,001$ properly). We developed math models to predict the probability of obesity depends on the DA and L concentrations. These models had high percentage of correct predicted values (86.7 – 90.4%), applied to prognosis the probability of a progressive childhood obesity and its variants (AO and EO).
Conclusion
DA concentrations were associated to BMI and SDS BMI in children with obesity particularly in boys and LP subgroups ($P<0.05$). L levels had positive relationships with anthropometric indexes mostly in girls and EP participants ($P \leq 0.001$). Math models, based on the DA and L concentrations, allowed to predictthe probability of obesity (AO and EO) in children.

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The influence of obesity on changes in adipokines during the menstrual cycle

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The purpose of the menstrual cycle is to prepare the egg for fertilization and implantation. The changes and functions of the basic steroid hormones during the menstrual cycle are well known. However, changes to other hormones occur during the menstrual cycle as well, including those influencing the intake of food. These changes have been described inconsistently in the literature, especially considering differences in overweight and obese women. The aim of this study was to describe the relationships between hormones associated with food intake and steroid during the menstrual cycle, along with differences between normal-weight and overweight women. The study included 27 healthy women (average age 28.0±3.4 years) with regular menstrual cycles (cycle length 28±days) who did not use any pharmaceuticals. These women were followed for one menstrual cycle, with regular measurements of body composition parameters, blood samples taken (fasting between 0700 and 0800 h), and daily food intake noted. We analyzed the following steroid hormones: cortisol, cortisone, DHEA, 7α-OH-DHEA, 7β-OH-DHEA, 7-oxo-DHEA, pregnenolone, 17-OH-pregnenolone, testosterone, aldosterone, corticosterone, androstenedione, estrone, estradiol, estriol (LC-MS/MS), and progesterone (RIA); complex of hormones associated with food intake: c-peptide, ghrelin, GIP, GLP-1, glucagon, insulin, leptin, PAI-1, resistin and visfatin (immunoassay), and LH, FSH, SHBG (radioimmunoassay), glycemia, osteocalcin, and the lipid spectrum (immunoassay). According to BMI the women were divided into two groups: those with BMI up to 25 ($n=15$), and those with BMI 25–30 ($n=12$). The study was approved by the local Ethical Committee. The steroid hormones showed similar physiological changes during the cycles of both groups. 7β-OH-DHEA was higher during all cycle in normal weight women.17-OH pregnenolone and androstenedione were higher in the overweight women. As expected, hormones associated with food intake, osteocalcin and SHBG were significantly different between the two groups. Leptin levels were significantly different in overweight women, and their profile lacked the typical consistent changes during the menstrual cycle. In contrast, while the adiponectin profile was similar in both groups, the levels of adiponectin were significantly higher in the overweight women.
Our study confirmed differences in the levels of certain hormones in overweight women during the menstrual cycle. These results should help improve our understanding of menstrual cycle problems that can occur in women after their weight increases.

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The effect of SNP (rs174537) in FADS1 gene on fatty acid composition in serum lipids

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Background
Fatty acid desaturase 1 (*FADS1*) gene controls the fatty acid metabolism pathway in the human body (Sergeant *et al*., 2012). Single nucleotide polymorphism (SNP) in *FADS1* gene and percentage of polyunsaturated fatty acids inserum lipids was associated (Klingel *et al*., 2018). Genetically predisposition to higher plasma arachidonic and stearic acid levels were associated with incidence oflarge-artery stroke and venous thromboembolism (Yuan *et al*., 2019).
Methods
Samples obtained in the COPAT project (Childhood Obesity Prevalence And Treatment) were used. Genomic DNA was extracted from peripheral blood leucocytes in whole blood samples. For genotype analysis TaqPath (LC480, Roche) was used. Sample of 754 adolescents (376 girls and 378 boys) from the Czech Republic was examinated in this project. Association of SNPs with fatty acid composition was conducted using the SIMCA-P12 (Umetrics, Umea, Sweden).
Results
The relationship of the risk allele (rs174537) with 12 fatty acids was significant. In SNP (rs 174537) has been relationship between risk allele and two fatty acids (20:4 n-6; 18:3 n-6) in all three lipid classes.
Conclusion
Single nucleotide polymorphisms (rs174537) in *FADS1* gene had a significant negative relationship with two fatty acids, (20:4 n-6 and 18:3 n-6), in all three lipid classes.
Conflict of Interest
None Disclosed.
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The educational training to the Mediterranean diet-like pattern is followed by improvement in cardiometabolic parameters and ecology of the microbiome in children with obesity: Preliminary results of the GOOD DAY trial

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Introduction
In the pediatric population the progression of obesity-related diseases can be delayed or prevented through changes in lifestyle, including the promotion of a Mediterranean-like dietary (MD) pattern.
Objective
We aimed to assess the efficacy of an educational training to MD based on gamification with respect to a conventional weight-loss treatment in obese

pediatric subjects on weight decreased and cardiometabolic risk factors (GOOD-DAY Trial; NCT03154255). We also aimed to evaluate the modulation of gut microbiome ecology with respect to dietary changes and clinical parameters.
Methods
A total of 67out of planned 80 subjects (6 and 18 years) with obesity, diet naïve or with failure to a previous weight loss program have been already recruited. We collected auxological, metabolic and nutritional parameters (KIDMED score; IDEFICS food frequency questionnaire) every 3 months for 24 months. Stools were collected three times: at T0, after six months (T2), and 12 months (T4) of interventions (gamification on MD, GAME, or conventional diet loss program, NO GAME). DNA was extracted directly from 0.25 g of stool using the Power SoilRKit. DNA was amplified with primers for the V3 and V6 regions of 16S rDNA tagged with Multiplex Identifier sequences using Microbiota Solution B Kit optimized for Illumina Miseq sequencing. Raw FastQ sequences were analyzed using MicrobAT Software. Statistical analyses were performed using R software. Metabolomic analyses are ongoing.
Results
We present clinical data of the first 35 subjects who ended the study. The microbiome data were analyzed for all the subjects at baselines and 14 out of 35 who concluded the study at T2 and T4. At baseline, clinical, metabolic characteristics and microbial communities were homogeneous among children; unclassified *Prevotella sp*. were more present in prepubertal subjects. All the children decreased their weight, waist circumference ad glucose levels at fasting at T4. Total and LDL cholesterol decreased, and HOMA-beta increased only in GAME children at T4, irrespective of weight loss. At T4, *Firmicutes*sp. increased and *Bacteroides sp*. decreased in the GAME group, diversely by NO GAME. The heatmap of the cluster revealed that, whether *Bifidobacterium adolescentis* increased in all the subjects over time, *Actinobacteria* and *Bifidobacterium longum subsp. null* also increased in the GAME group at T4.
Discussion
These preliminary results highlight the importance of adherence to the MD in weight loss, by improving some metabolic parameters. Gut microbiome seems could have a role on metabolic changes following lifestyle changes inspired to MD.

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Liraglutide downregulates the expression of miRNA-424 in patients with obesity

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Aims
Liraglutide 3 mg once daily is an approved, prescription injectable Glucagon Like Peptide-1 receptor agonist that, when used with a low-calorie diet and increased physical activity, can reduce excess weight in patients with obesity. MiRNAs are small non-coding single stranded RNAs that regulate gene expression post-transcriptionally by inhibiting their mRNA target translation into proteins. MiRNAs can be secreted in the blood stream and affect the molecular pathways of distal cells. Several studies have demonstrated that obese patients express a differential pattern of circulating miRNAs compared to lean subjects. The effects of liraglutide in circulating miRNAs remain largely unknown.
Methods
To investigate whether treatment with 3 mg liraglutide can affect the level of circulating miRNAs, we tested the expression of several miRNAs in the plasma of 16 obese patients enrolled in a clinical trial at baseline and after 8 weeks of treatment with qPCR analysis using the Locked Nucleic Acid technology. RNA was extracted using miRNeasy Serum/Plasma Advanced Kit (Qiagen) and reverse transcribed into cDNA using miRCURY Universal RT Kit (Qiagen). MiRNA expression was analysed using SYBR green (Sigma) and LNA primer assays (Qiagen). Cel-miR-39-3p and Unisp6 spike-ins were used as controls of RNA extraction and reverse-transcribed respectively to normalise the expression of the miRNAs of interest.
Results
At baseline, participants had a mean weight of 120.5 kg (±19.64) and BMI of 42.18 kg/m^2. At week 8, participants had lost a mean of –6.1 kg (S.D.± 2.39) of body weight ($P<0.01$). Among the tested miRNAs, expression of miR-424 was significantly ($P=0.008$) decreased after 8 weeks of treatment. Statistical analysis was performed using paired, two-tailed student t-test with level of significance set at $P<0.05$.
Conclusions
Although there has been growing interest in the roles of obesity induced miRNAs in insulin resistance and T2DM, their molecular targets and regulation mechanism are not completely understood. According to evidence, upregulated expression of miR-424 impairs insulin-signaling and insulin-induced glycogen synthesis in hepatocytes of patients with obesity. Herein we demonstrate that miR-424 induced by obesity is reduced after treatment with liraglutide and this could be a potential weight-loss independent mechanism of action by which liraglutide exerts its beneficial effects on insulin resistance.

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AEP375

Predictors of metabolic disease in normal weight postmenopausal women: A cross-sectional study

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Introduction
The aim of this study was to evaluate predictors of metabolic disease in normal weight postmenopausal women.
Patients and methods
This cross-sectional study included 457 non-obese postmenopausal women, recruited from the Menopause Clinic of Aretaieio Hospital, National and Kapodistrian University of Athens. The diagnostic criteria of the International Diabetes Federation for the definition of Metabolic Syndrome were used, in order to classify women into metabolically healthy (<3 criteria, MHNW) and metabolically obese (≥3 criteria, MONW).
Results
Compared to the MHNW phenotype, MONW was positively associated with chronological age (58.9±7.9 years vs 54.3±6.6 years, $P<0.001$), years since menopause (YSM, 12.4±8.5 years vs 7.1±6.2 years, $P<0.001$), waist circumference (WC, 92.1±6.6 cm vs 82.3±8.4 cm, $P<0.001$) and waist to hip ratio (WHR, 0.87±0.06 vs 0.81±0.08, $P<0.001$). ROC curve analysis showed that WC represents a superior predictor of MONW compared with WHR (WC, AUC 0.815, 95% CI 0.773–0.858). Accordingly, WC of at least 86.5 cm predicted the MONW phenotype with sensitivity 72.7% and specificity 69.4%. Multivariate regression analysis showed that WC of at least 86.5 cm predicted the MONW phenotype in a model adjusted for age and YSM (OR 4.689, 95% CI 2.626–8.373, $P<0.001$).
Conclusions
This study provided evidence that MONW women have increased chronological age and YSM compared with MHNW women. Metabolic disease can be predicted by a WC greater than 86.5 cm, irrespectively of age and YSM.

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Phase angle (PA) and body composition changes in obese patients with associated comorbidities (by AACE criteria) through a very low calorie diet (VLCD) program

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Introduction
Obesity is defined as a chronic disease by AACE/ACE. Includes presence/severity of complications. VLCD diets induce relevant weight loss by improving these complications. PA is a bioelectric measure of the cell mass and it is marker a global prognostic factor of cellular functionalism.
Methods
Case-control retrospective study of severe obesity in a weight loss program comparing intensive intervention (41 cases, VLCD 800 kcal/d, 1g protein/kg) vs conventional (22 controls, cardiac rehabilitation program with Mediterranean diet and exercise). Clinical variables (AACE), anthropometric (impedance measurement), analytical and pharmacological changes are measured.
Objective
To evaluate anthropometric changes, body composition and bioelectrical measures such as PA, resistance (Rz) and reactance (Xc), analytical changes and effects on obesity complications and therapeutic changes in both groups.
Results
Average age in cases 58.0±13.5 years, (59% women) with a BMI of 46.3±10.0 kg/m^2. 79.3% arterial hypertension, 93% carbohydrate alterations (82.7% T2DM, 10.3% Prediabetes), 82.8% dyslipidaemia, 44.5% steatosis, 10.3% polycystic ovary, 55.1% SAHS, 55.2% osteoarthritis, 27.5% gastroesophageal reflux, 34.5% urinary incontinence, 20.7% immobility, 86.2% psychological disorder. 55% used ≥3 antihypertensive drugs, 48% insulin, 59% statins and 18% fibrates. 6 months after intervention: We observed a weight loss of 16.9±12.8 kg with a BMI reduction of 6.24±4.69 kg/m^2 in cases compared to –2.7±0.9 kg and –0.92±0.3 kg/m^2 in controls. In cases, there was a decrease in Fat-Mass (FM) of – 14.7±10.2 kg with a slight decrease in Fat-Free-mass (FFM) –2.3±7.0 kg and a rise in Body-Cell-Mass (BCM)+3.0±6.4 kg. In VLCD group, there was a significant increment in PA+1.18±0.98 associated with an increase in Rz +35.0±59.9 and Xc +11, 8±10.2 (P<0.05), related with hydration –3.8±4.6% and nutrition changes+93.0±195.2 Ucr/m, without changes in control group. An important improvement in glycaemia, cholesterol, triglycerides, transaminases and microalbuminuria was evident in both groups, being more relevant with intensive intervention. Reduction HbA1c 2.1±0.4% (P<0.001) vs 0.4±0.4% (P=0.36).
Conclusions
VLCD produces an improvement in body composition (PA and BCM) with reduction in obesity complications (2 stage of AACE), associated a reduction in treatments needs (insulin therapy suspension in 84% of cases, reduction in others drugs) and metabolic changes (HbA1c): fundamental objectives in the intervention.

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AEP377

The additive effect of obesity in the incidence of neurocognitive disorders in offspring of women with gestational diabetes

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Aim
Gestational diabetes (GDM) has been associated with an increased risk ofneurocognitive outcomes in offspring such as attention deficit/hyperactive disorders (ADHD) and autism spectrum disorders (ASD). However GDM-related comorbidities (obesity or excessive weight gain –EWG-) in this setting have been scarcely studied. So, the aim of our study was to estimate the risk of ADHD and ASD in this population.
Material and methods
Cohort study. Singleton pregnancies complicated by GDM between 1991–2008 were selected. Maternal data was prospectively collected during pregnancy. ADHD and ASD diagnostic was obtained from medical records. Cox proportional hazards modeling adjusting for potential confounders were applied to estimate the effect of maternal obesity and EWG during pregnancy.
Results
A total of 1118 pregnancies were selected. The median follow-up was 17.5 years [14.5–21.4] with 12% (n=142) and 0.01% (n=14) of subjects diagnosed of ADHD and ASD, respectively. As table 1 shows, maternal obesity increased the risk of ADHD. EWG was only associated with increased risk of ADHD in the early-GDM subgroup. Neither maternal obesity nor EWG were associated with ASD. Insulin use during pregnancy did not modify the results.

Table 1

		Total cohort (n=1118)	Early GDM (n=202)	Late GDM (n=916)
ADHD	**Maternal weight (kg/m²)**			
	18.5–24	Ref.	Ref.	Ref.
	<18.5	0.61[c] (0.09–4.40) 0.63[a] (0.09–4.53)	7.19[c] (0.83–62.15) **11.80[a] (1.26–110.0)**	–
	25–29	1.26[c] (0.85–1.86) 1.21[a] (0.81–1.81)	2.82[c] (0.94–8.42) 3.21[a] (0.99–10.31)	1.08[c] (0.70–1.67) 0.99[a] (0.63–1.54)
	≥ 30	**1.74[c] (1.16–2.62)** **1.68[a] (1.11–2.55)**	1.62[c] (0.51–5.10) 1.83[a] (0.55–6.10)	**1.93[c] (1.22–3.05)** **1.84[a] (1.16–2.94)**
	EWG	**1.52[c] (1.02–2.58)** 1.46[a] (0.97–2.20)	**2.73[c] (1.13–6.59)** **3.53[a] (1.37–9.14)**	1.23[c] (0.76–1.97) 1.16[a] (0.69–1.81)
ASD	**Maternal weight (kg/m²)**			
	18.5–24	Ref.	Ref.	Ref.
	<18.5	n/a	n/a	n/a
	25–29	1.90[c] (0.55–6.59) 2.36[a] (0.66–8.42)	n/a	1.61 (0.43–5.98) 2.42 (0.61–9.58)
	≥ 30	2.37[c] (0.63–8.82) 2.76[a] (0.72–10.6)	n/a	0.80 (0.09–6.91) 0.66 (0.074–6.11)
	EWG	0.44[c] (0.57–3.42) 0.64[a] (0.08–5.20)	2.09[c] (0.18–23.08) 3.14[a] (0.26–38.60)	n/a

Data was expressed as Hazard Ratio and 95% Confidential Interval. [c]: crude model. [a]: adjusted model including maternal age at pregnancy, weeks of gestation, C-section, Apgar <3 at min 1 or 5, small for gestational age (percentile <10) and current smoking during pregnancy.
ADHD: attention deficit/hyperactive disorder. ASD: autism spectrum disorder. EWG: excessive weight gain during pregnancy according to OMS criteria. Early/Late gestational diabetes mellitus (GDM): diagnosed </≥ 26 weeks of gestation, respectively.

Conclusions
Beyond deleterious effect of hyperglycaemia, maternal weight itself plays a role increasing the risk of ADHD in offspring. Regarding ASD, the low number of subjects did not allow reliable conclusions.

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AEP378

Bariatric surgery impact on cardiovascular risk factors: Is age a factor to consider?

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Introduction
Despite the abundance of data addressing the influence of patient's age on surgery-related complications, its impact on several cardiovascular risk factors following bariatric surgery has been overlooked.
Methods
Retrospective unicentric study of 1728 obese patients who underwent bariatric surgery between January/2010 and June/2015. Patients were divided in three groups, according to their age at surgery: <40 (n=751), 40 to 59 (n=879), and ≥60 years old (n=98). Parameters with cardiometabolic impact, such as body anthropometric measures, lipid profile, and glycemic status, before and 24 months after surgery, were compared between these groups. A multiple linear regression was performed, adjusting differences between groups for sex, surgery type, and body mass index (BMI) variation.
Results
The group <40 years old presented more weight loss (–35.4±9.0 kg, P<0.001), greater BMI reduction (–15.8±6.1 kg/m^2, P <0.001), and larger changes in waist (–34±13.8 cm, P<0.001) and hip circumferences (–28.7±11.9 cm, P<0.05).The group of ≥60 years old presented the heaviest reduction in fasting glucose (–23.3±11.0 mg/dl, P<0.001) and A1c

(–0.7±1.0%, $P<0.001$), and also had a tendency to have the biggest changes in systolic blood pressure (–14.7±18.7 mmHg; $P=0.071$).
Conclusion
Patients with ≥60 years old benefit the most from bariatric surgery regarding parameters with cardiometabolic impact, presenting heavier reductions in fasting glucose as well as A1c, and a tendency towards a higher decrease in systolic blood pressure. No clinically-significant differences in lipid profile were observed between groups.

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AEP379

TGFβ1 downregulates hepatic SHBG production by decreasing HNF-4α levels via SMAD and STAT3 pathways

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Low plasmasex hormone-binding globulin (SHBG) levels are present in fatty liver disease, which represents a spectrum of diseases ranging from hepatocellular steatosis through steatohepatitis to fibrosis and irreversible cirrhosis. We are interested in studying the molecular mechanisms by which plasma SHBG levels are reduced in fatty liver disease. In this regard, we have previously shown that fat accumulation in the liver reduces SHBG production by reducing hepatic nuclear factor 4 alpha (HNF-4α), a main regulator of SHBG expression. Transforming growth factor β1 (TGFβ1) plays an important role in the pathogenesis of liver fibrosis, being involved in activation of hepatic stellate cells, stimulation of collagen gene transcription, and modulation of matrix metalloproteinase expression. The aim of the present studywas to evaluate the role of TGFβ1 in regulating hepatic SHBG production. For this purpose, *in vitro* and *in vivo* studies were performed using human HepG2 cells and human *SHBG*transgenic mice. Our results showed that TGFβ1 treatment reduces SHBG production (mRNA and protein) in HepG2 cells. In addition, human *SHBG* transgenic mice treated withTGFβ1 showed a significant reduction SHBG expression as well as in plasma SHBG levels. Mechanistically TGFβ1 downregulates HNF-4α levels via SMAD and STAT3 pathways through TGFβ1 receptor I. Taking together, we found for the first time that TGFβ1 regulates hepatic SHBG production. These results may explain why patients with fibrotic livers show low plasma SHBG levels.

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AEP380

Cryptogenic cirrhosis and metabolic syndrome: What relationship?

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Introduction
Cryptogenic cirrhosis is cirrhosis that remains of unknown etiology after an exhaustive investigation. The relationship of cryptogenic cirrhosis with metabolic syndrome is strongly suggested. The aim of this work was to study the clinical-progressive profile of cryptogenetic cirrhosis and to determine the frequency of the metabolic syndrome.
Patients and methods
This is a study collecting all cirrhotic patients over a period of 4 years in our gastroenterology department. The patients were divided into 2 groups (group 1 (G1): cryptogenic cirrhosis and group 2 (G2): cirrhosis of known etiology).
Results
A total of 71 patients were collected with an average age of 62 years. Viral origin was the most common cause (40.2%). Cirrhosis was classified as cryptogenic in 26.7% of cases ($n=19$). Metabolic syndrome was more common in group 1 with a significant difference (68.4% vs 30.4%, $P=0.006$). In group 1 patients, at least one criterion of the metabolic syndrome was found: diabetes (68.4%), hypertension (21.05%), dyslipidemia (10.5%) and overweight (73.6%)). Biologically, more than half of the patients in group 1 (57.8%) had disturbances in the liver balance: cytolysis in 21.05%, cholestasis in 15.8% and an isolated increase in GGT in 21, 05% of cases. By comparing the 2 groups, no significant difference was found in terms of sex, age and complications of cirrhosis except hepatocellular carcinoma which was more frequent in patients in group 2 with a significant difference ($P=0.05$).
Conclusion
Cryptogenetic cirrhosis and metabolic syndrome are strongly associated. This association argues in favor of the role of non-alcoholic steatohepatitis as the main cause of cryptogenetic cirrhosis. This association also does not expose to a greater risk of complications.

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AEP381

Association of osteoprotegerin and metabolic status in children with obesity

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Objective
Determination of changes in metabolic status and osteoprotegerin concentrations in obese children.
Methods
We examined 221 children in the University Hospital (Minsk) from 2017 to 2019 yrs. Their anthropometric parameters (height, weight, body mass index (BMI)) were determined. Blood levels of osteoprotegerin (OPG), insulin were determined. In the biochemical blood test, the parameters of uric acid, insulin were evaluated. All children were divided into 2 groups: group 1 children with morbid obesity – 159 patients (98 boys(B)/61 girls(G)) (BMI more than 99th percentile for sex and age) (BMI 32,95±4,61 kg/m^2, age 14,16±2,28 years); group 2 – 62 patients (B/G=31/31) with alimentary obesity (BMI-95-99th percentile for sex and age) (BMI 27.86±2.04 kg/m^2, age 14.77±2.05 years). The control group consisted of 84 patients (B/G=45/39) with normal body weight (BMI 19.86±2.24 kg/m^2, age 14.32±2.11 years).
Results
In the subgroups of boys with obesity, there were significant differences in the concentration of uric acid in comparison with the control (alimentary obesity 426.55±62.25 mmol/l vs 242.58±49.90 mmol/l ($P=0.01$)), morbid obesity 324.10±59.33 mmol/l vs 242.58±49.90 mmol/l ($P=0.01$)). Girls with obesity have a significant increase in uric acid level in comparison with the control group (alimentary obesity 328.10±51.43 mmol/l vs 213.0±39.64 mmol/l ($P=0.0001$), morbid obesity 409.04±84.23 mmol/l vs 213.0±39.64 mmol/l ($P=0.0001$)). In boys with obesity higher concentrations of OPG were detected relative to the control group (alimentary obesity 259.98±108.07 ng/ml vs 225.12±55.88 ng/ml ($P=0.09$), morbid 322,22±82,14 ng/ml vs 225.12±55.88 ng/ml ($P=0.001$)). In girls with obesity higher concentrations of OPG were detected relative to the control group (alimentary obesity 326.84±104.02 ng/ml vs 254,39±78,29 ng/ml ($P=0.046$), morbid 347.33±93,50 ng/ml vs 254.39±78.29 ng/ml ($P=0.03$)). In boys with obesity higher concentrations of insulin were detected relative to the control group (alimentary obesity 18.9±12.7 μU/ml vs 9.1±4.2 μU/ml ($P=0.0001$), morbid 28.71±7.36 μU/ml vs 9.1±4.2 μU/ml ($P=0.001$)). In girls with obesity, the concentration of insulin relative to the control group was (alimentary obesity 20.28±6.25 μU/ml vs 14.10±6.80 μU/ml ($P=0.001$)) morbid obesity 23.32±9.65 μE/ml vs 14.10±6.80 μU/ml ($P=0.001$)).
Conclusion
Children with obesity have an increase in insulin and OPG rates.

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AEP382

Different effects of 5α-dihydrotestosterone treatment on hepatic and visceral adipose tissue inflammation in animal model of polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is a complex reproductive disorder that is usually associated with metabolic disturbances such as obesity, dyslipidemia and insulin resistance. In this study, female rats treated with nonaromatizable 5α dihydrotestosterone (DHT) were used as an animal model of PCOS. The aim of this study was to assess the presence of inflammation

in liver and visceral adipose tissue (VAT), which accompanies metabolic disturbances in animal model of PCOS. Female (21 days old) Wistar rats were treated subcutaneously with DHT pellets, while control animals received placebo pellets. Glucose, triglycerides, free fatty acids (FFA) were determined in blood plasma, while corticosterone was analyzed both in plasma and liver. Expression of genes and proteinsinvolved in lipid metabolism, such as sterol regulatory element binding protein1 (SREBP-1), fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC), lipin-1, adipose tissue triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), were analyzed in the VAT of treated rats. Tissue inflammationevaluated by nuclear factor kappa B (NFκB)protein level and intracellular distribution, as well as by TNFα, IL6 and IL1β mRNA levels. Glucocorticoid signaling was examined at the level of 11 beta hydroxysteroid dehydrogenase type 1 (11βHSD1) and 5α-reductase, as well asby glucocorticoid receptor (GR) leveland its subcellular distribution. The results showed that DHT treatment induced increase of lipogenic factors (SREBP-1, lipin-1, FAS and PEPCK), while the level of lipolytic enzyme HSL was decreasedin VAT. These molecular alterations were accompanied by adipocyte hypertrophy, visceral obesity and elevated plasma FFA and triglyceride concentrations. Those changes in lipid metabolism were possible trigger for low-grade inflammation observed in the VAT and characterized by NFκB activation and increasedIL6 and IL1β mRNA levels. In spite of increased VAT proinflammatory mediators, the level of proinflammatory cytokines, IL6 and IL1β, was decreased in the liver of DHT-treated rats, while the activation of NFκB remained unchanged. The state of suppressed inflammation in the liver could be an outcome of stimulated glucocorticoid signaling, as judged byincreased hepatic corticosterone level and GR activation. The augmentation of hepatic glucocorticoids could be a net result of increased expression of 11βHSD1 and decreased expression of 5β-reductase mRNA. In conclusion, the results showed that abdominal obesity and dyslipidemia in the animal model of PCOS were accompanied with hypertrophic adipocytes, lipid accumulation and low-grade inflammation in the VAT. However, these metabolic disturbances did not resultin hepatic inflammation due to increased tissue levels of glucocorticoids.

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AEP383

Association of AdipoQ gene & its expression in adipose tissue with post prandial hypertriglyceridemia and glucose intolerance

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Background
AdipoQ gene is located at the 3rd chromosome and encodes foradiponectin which is involved in fat metabolism and insulin sensitivity and plays a protective role in diabetes and atherogenesis. AdipoQgene variants have been reported to be associated with hypertriglyceridemia and risk of diabetes in different studies. We aimed to study whether polymorphism of rs2241766 polymorphic form of AdipoQ gene & its expression in adipose tissue is associated with post prandial hypertriglyceridemia and glucose intolerance.
Methodology
Polymorphism study of AdipoQ gene rs2241766 was carried out by using PCR-RFLP method in 200 age and sex matched subjects who were recruited in three groups {NGT ($n=67$), Prediabetes($n=66$) and T2DM($n=67$} with varying glucose tolerance following 75 gm OGTT. Gene expression studies using Real Time PCR were also done in subcutaneous and omental adipose tissue in 10 subjects from each group who were scheduled to undergo abdominal surgery. A Standardized oral fat challenge test was performed in all the study subjects to determine their post prandial Tg responses besides measurement of anthropometric (BMI, Waist) and Glycaemic (Fasting, Postprandial plasma glucose and HbA1c) indices and fasting serum insulin.
Results
The mean age of study subjects were 40.25±8.27 years and their mean BMI was 28.12±4.89 kg/m^2. There were 93 males and 107 females. TT geno types of rs2241766 polymorphic form of AdipoQ gene showed significantly lower 2 hr PPTg (190±84 vs 244±98 mg/dl $P=0.008$), Triglyceride area under curve (2445±1139 vs 2993±1436 mg dl^{-1} 2 hr^{-1} $P=0.05$), fasting-plasma glucose (99±13 vs 111±35 mg/dl $P<0.001$) and postprandial plasma glucose (140±46 vs 173±79 mg/dl $P=0.002$) as compared to GG+GT genotypes. Distribution of TT genotype of rs 2241766 polymorphic form of AdipoQ gene was found to be significantly lower inthe T2DM subjects (71% vs 79% $P=0.01$) as compared to NGT subjects. AdipoQ gene expression was 3.1 fold lower in prediabetes group ($P<0.01$) and 2.6 fold lower in T2DM group ($P=0.003$) as compared to NGT group in subcutaneous adipose tissue which correlated significantly with postprandial plasma glucose levels ($r=-0.48$ $P<0.04$)
Conclusion
The findings of the present study indicate that TT allele of rs2241766 polymorphic form of AdipoQ gene is associated with lower postprandial triglyceride levels and a lesser degree of glucose intolerance in Asian Indian subjects. Glucose intolerant subjects also display lower AdipoQ gene expression in adipose tissue.

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AEP384

Evaluation of macrovascular complications with Ankle-Brachial index in Type 2 diabetes

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Aim
In our study; we aimed to evaluate the relationship between Ankle-brachial index (ABI) values and diabetes duration, and macrovascular complications in patients with DM with demographic data, anthropometric measurements, as well as clinical and laboratory data.
Materials and methods
Our study is a cross-sectional study of 226 randomly selected DM patients who were admitted to the diabetes outpatient clinic of our hospital between April 2019 and October 2019. All patients' data, such as age, sex, height, weight, waist and hip circumference, wrist and ankle circumference, family history, DM duration, chronic disease history, claudication, neuropathy, diabetic foot ulcer history, as well as routine blood and urine examinations at control were recorded. In addition, ABI was also measured in patients. Patients with ABI values of ≤0.90 were classified as PAD-positive, and those with >0.90 were classified as PAD-negative. The data, measurements and metabolic parameters we obtained, were evaluated to determine whether they are risk factors for ABI value, their association with ABI value, and differences according to ABI value.
Results
A total of 226 patients (138 female, 88 male) with a mean age of 52.8±10.3 years were included in the study. ABI was positive in 29.2% of the patients. There was no significant difference in ABI value between age, sex, family history, body mass index (BMI), waist circumference and duration of diabetes. A significant correlation was found between ABI and coronary artery disease ($P=0.004$), diabetic foot ulcer ($P=0.000$), smoking ($P=0.000$) and wrist circumference ($P=0.026$). No significant correlation was found between ABI value and glycylated hemoglobin A1c (HbA1c), low density lipopretein (LDL) cholesterol, triglyceride, non-high density lipoprotein (non-HDL) cholesterol levels and atherogenic index. Logistic regression analysis revealed that diabetic foot, coronary artery disease, BMI, duration of diabetes and HbA1c had a negative impact on ABI.
Conclusion
In our study, we obtained positive ABI values consistent with PAD in 29.2% of patients, suggesting that each patient with DM should be evaluated for PAD. Among patients with diabetes, those with a history of diabetic foot ulcers and/or cardiovascular disease, obesity, long duration of diabetes and patients with increased HbA1c levels under treatment, are considered as priority groups for peripheral arterial disease.
Keywords: peripheral artery disease, diabetes mellitus, ankle-brachial index.

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AEP385

Maternally inherited diabetes and deafness presenting as diabetic ketoacidosis

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Background
A 29 year old female presented to the Emergency department with headache, vomiting and loose stools for 24 hours. She was not known to have diabetes. She had a background of bilateral sensorineural deafness for 6 years and

resolved Gillian Barre syndrome 8 years prior. She has a family history of deafness and diabetes mellitus in her maternal grandmother and mother; and diabetes in her maternal aunty and two maternal uncles diagnosed with pre-diabetes. She has a partner and two children aged two and nine years with no history of diabetes or deafness.
Investigations and management
On admission her blood glucose was 22.3 mmol/l, blood ketones were raised (4.9 mmol/l), low blood low PH (6.836) and low bicarbonate (5.7 mmol/l). Other investigations were as follows: WCC 19.2, serum sodium 130 mmol/l, creatinine 68 umol/l; calcium 2.15 mmol/l, magnesium 0.50 mmol/l, HbA1c 26 mmol/mol, vitamin B12 114 ng/l, folate 7.0 mg/l, ferritin 40 mg/l and negative pregnancy test. Examination revealed low BMI (18.3) with no signs of infection on systemic examination. Patient was managed as Diabetic Ketoacidosis with fixed rate insulin infusion followed by variable rate insulin infusion. She was then assessed by the diabetic team and started on basal-bolus insulin regime; diabetes education provided on discharge. Further investigations revealed negative Anti-GAD antibodies, negative Anti-islet cell antibodies, negative TTG IGA, normal Thyroid function test. Patient is managed by Diabetes Community team and awaiting results from genetic testing for MIDD.
Discussion
Type 1 and Type 2 diabetes constitute the most common types of DM. With increasing insight into genetic medicine, monogenic diabetes has gained interest as rare aetiology of adult onset diabetes. Maternally Inherited Diabetes and Deafness is caused by mitochondrial DNA defect accounting for 1% of diabetes mellitus. A to G (adenine to guanine) substitution at 3243 is the most common associated DNA mutation which then results in defective oxidative production of energy. Salient features comprise of Diabetes, Deafness, Maculopathy and Positive family History of Deafness and Diabetes. Other features consist of left ventricular failure, focal segmental glomerular sclerosis. Approximately 20% present as type 1 DM and 8% as DKA. Diagnosis involves genetic testing of 3243 A>G mutation in blood or urine sample. Management includes early recognition and prevention of systemic complications by commencing patient on appropriate treatment and regular follow up.
Conclusion
Clinicians should have low threshold for suspecting MIDD in a patient with low BMI, Anti Gad negative and a family history of Diabetes and Deafness.

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AEP386

Association of depressive symptoms and diabetes-related distress with glycemic control, self-care activities and quality of life in diabetic patients

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Background
Depressive symptoms (DS) and diabetes-related distress (DD) are common comorbidities in diabetic patients adversely affecting diabetes self-management and patients' well-being.
Aim
To examine associations between DS and DD with glycaemic control, quality of life and diabetes self-management.
Materials and methods
Depressive symptoms, DD, quality of life, diabetes self-management and metabolic indicators were assessed in 148 participants included in a Day Hospital educational programme (aged 42±15 years, 57% female, 78% T1 diabetes) at baseline and after a one-year follow-up. Associations between these variables were analysed in patients with: 1. depressive symptoms (n=26), 2. diabetes-related distress (n=14), 3. both symptoms (n=19), and 4. without symptoms (n=89) by using Kruskal-Wallis test. Prognostic value of the included variables for one-year metabolic outcomes was determined by regression analysis.
Results
The groups differed with respect to health-related quality of life and diabetes self-management: examinees without symptoms reported better quality of life (Kruskal-Wallis H=10,4 P=0,02; H=52,9 P<0.01) and better adherence to diet (H=8,9 P=0,03), self-monitoring blood glucose (H=7,9 P=0,05) and exercise (H=12,3 P<0,01). Metabolic indicators did not differ between the groups. Examinees without emotional symptoms improved their HbA1c (7.6%±1.2 vs 7.3%±1.1 P=0,04) during a follow-up period while other groups did not. Diabetes-related distress was shown to be a long-term predictor of metabolic control (stand. ß=.228 P=.025), while quality of life could be predicted by DS (stand.ß=–.422 P<.0001) and DD (stand.ß=–.329P<.0001; stand.ß=–.459 P<.0001).
Conclusion
Depressive symptoms and DD are longitudinally associated with patients' quality of life, diabetes self-management and diabetes control. Both symptoms should be recognized in order to establish an appropriate clinical approach.

Keywords: diabetes, depressive symptoms, diabetic-related distress, glycemic control, self-management of diabetes, quality of life.
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AEP387

Albuminuria and carotid intima-media thickness as surrogate markers of atherosclerosis in asymptomatic patients with type 2 diabetes

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Introduction
Clinical assessment of atherosclerotic complications in type 2 diabetes mellitus (DM) was diverted to the detection of subclinical form of atherosclerosis using the non-invasive diagnostic methods. Surrogate markers of subclinical atherosclerosis are carotid intima-media thickness (IMT) and albuminuria. The aim of this study was to analyze a relationship between the presence of albuminuria and carotid IMT in patients with type 2 DM and silent ischemia.
Methods
Our study included 62 patients, aged 40–70, with type 2 diabetes, without previous history of cardiovascular disease. The patients performed exercise stress test and based on the results, were divided into two groups. The first group consisted of 25 patients with ischemic heart disease (IHD), whereas the second group consisted of 37 patients without IHD. In all patients, we measured IMT with ultrasound and albumin in 24-hour urine. The obtained values were compared between the groups.
Results
Patients with IHD were older, with a longer duration of diabetes, dyslipidemia and higher level of HbA1c compared to the control group without IHD (P<0.05). There was a statistically significant higher value of carotid IMT in the group of patients with IHD (1.08±0.17 mm) compared to those without IHD (0.78±0.17 mm) (P<0.001). The presence of albuminuria was significantly higher in the study group with IHD (22 patients) compared to the control group (9 patients), which has a statistical significance (P<0.001). In patients with IHD albuminuria was present in 22 and in patients without IHD in 9 patients, which was statistically significantly higher in the group of patients with IHD compared to the control group (P<0.001).
Conclusion
Patients with increased carotid intima-media thickness and albuminuria have a greater risk of IHD.

Keywords: diabetes mellitus, intima-media thickness, albuminuria.
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AEP388

Exacerbations of psoriasis in patients with type 2 diabetes

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Psoriasis patients have an increased risk of cardiovascular disease, stroke, hypertension, and type 2 diabetes (T2D). External factors (infections, stress, trauma, endocrine diseases) can trigger psoriasis. Skin diseases in patients with T2D are increased, hyperglycemia leads to damage to vascular intima. Itching of the skin leads to disruption of the repair and regeneration.
Objective
To study the influence of T2D on the exacerbations of psoriasis.

Materials and methods
We studied hospitalized patients with T2D and psoriasis in dermatological clinic during 5 years ($n=47$)-the main group. Comparison group 1-patients with psoriasis without T2D ($n=40$), comparison group 2-patients with T2D without psoriasis ($n=37$). Patients were excluded: with the psoriatic arthritis, GFR ≤ 45 ml/min/1.73 m^2.
Results
Patients of the main group (women-53.2%, men-46.8%, mean age 61.0±7.7 years), comparison group 1 (women-55%, men-45%, mean age 60.5 ±7.5 years), comparison group 2 (women-54%, men-46%, mean age 62.0±7.8 years) were same in clinical, anthropometric, anamnestic and laboratory data (AST, ALT, total cholesterol, creatinine, $P>0.05$). Patients of the main group and comparison group 1 differed in serum glycemia ($P=0.005$). Patients of the main group had an increase HLA1c level (11.8 (7.9–12.3)) compared with the comparison group 2 (6.8 (6.1–7.3), $P=0.006$) in the exacerbation of psoriasis period.
The number of hospitalization in 5-year period was in 2.6 times higher in patients of the main group – 55 cases (1.17 exacerbations / person for a 5-years period), in the comparison group 1–18 cases (0.45 exacerbations/ person for a 5-years period).
Conclusions
Psoriasis exacerbations in patients with psoriasis and type 2 diabetes were in 2.6 times often in 5-year period compared with psoriasis without type 2 diabetes. There is probably a correlation between psoriasis exacerbation and type 2 diabetes decompensation.

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Disordered eating behaviour in type 2 diabetic patients receiving oral hypoglycemic drugs

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Objective
Patients with type 2 diabetes mellitus (DM) are expected to follow numerous dietary recommendations which can be difficult to adhere and that can cause changes in their eating behavior. Few studies have examined prevalence rates eating disorders in adults with type 2 DM despite the fact that DM is highly correlated with overweight and obesity. The aim of the study was to assess the prevalence of disordered eating behavior in type 2 diabetes mellitus patients received oral hypoglycemic agentsusing EAT-26 questionnaire
Method
342 patients with type 2 diabetes mellitus receiveing oral hypoglycemic agentswere examined. The mean age 64 (58–69) years, mean body mass index (BMI)- 31.6(28.4–35.1) kg/m^2, duration of diabetes mellitus was 6(2–10) years. The group of women consisted of 223 patients (the mean age 64 (58–50) years, the mean BMI 31.6 (28.6–35.7) kg/m^2, the mean duration of DM 6 (5–10) years, the group of men include 108 patients, mean age 63 (56.5–68) years, BMI 31.3(28.3–33.9) kg/m^2, duration of DM 6 (2–10) years. There were no statistic differences in age (U=11088, 5 $P=0.077$), BMI (U=11659.0 $P=0.276$), duration of DM (U=8461.5 $P=0.800$) in the subgroups. The EAT-26 questionnaire was used in order to identify the high-risk subjects for eating disorders. The cut off 20 was used as a criteria for diagnosis.
Results
The prevalence of disordered eating behavior according to the results of cut off EAT-26 questionnaire in type 2 DM patients was 18.1% (62 of 342 patients had the score 20 and higher). The mean score of EAT-26 was 11(6–16). Statistical differences were revealed in the EAT –26 score depending on gender (U=10026.0 $P=0.002$). The mean EAT score in subgroup of men was lower 9 (5–14) than in the subgroup of women 12 (7–17). The prevalence of disordered eating in the subgroup of men was 14.8% (16 of 108 patients). In the subgroup of women 20.6% (48 of 233 patients).
Conclusion
The prevalence of disordered eating behavior in type 2 DM patients tested by EAT-26 questionnaire was 18.1% (in the subgroup of men 14.8%, in the subgroup of women 20.6%).

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Insulin need and determinants of insulin usage in diabetes mellitus during pregnancy

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Aim
We aimed determinants of insulin usage in pregnant women with impaired carbohydrate metabolism (ICM).
Methods
We collected 164 pregnant women in any trimester who were referred to endocrinology unit due to suspicion of ICM by obstetricians. Diagnostic laboratory criteria were as follows: fasting glucose ≥126 mg/dl in first trimester; 1 hour 50 g challenge test glucose ≥180 mg/dl; any value exceeding threshold during OGTT (fasting glucose ≥92 mg/dl, 1 hour glucose ≥180 mg/dl, 2 hour glucose ≥153 mg/dl). Those with previous diagnosis of DM were also included. Insulin therapy was initiated in case of measurements exceeding target values (at least 2 fasting glucose ≥95 mg/dl and either 1 hour or 2 hour postprandial glucose ≥140 mg/dl ≥120 mg/dl, respectively) despite medical nutrition therapy.
Results
Mean and S.D. values were: age 31.4±4.7 years, gestational age (GA) at initial visit to endocrinology unit 25.9±5.2 weeks, GA at initiation of insulin 26.7±7.8 weeks, number of pregnancies 2.3±1.4, TSH 1.76±1.21 mIU/l, and hemoglobin A1c 5.82±1.06%. Insulin users ($n=90$) had higher fasting glucose ($P=0.001$), 2 hour OGTT-glucose level ($P=0.004$), and hemoglobin A1c ($P=0.001$) at diagnosis in comparison to non-insulin users ($n=74$). Insulin users who gave birth before 36 weeks had higher hemoglobin A1c than those after 36 weeks (6.32±1.68% vs 5.62±1.68%, $P=0.014$). GA at diagnosis was positively correlated with GA at insulin initiation ($r=0.634$, $P=0.001$). GA at diagnosis was significantly lower in subjects who gave birth before 36 weeks in comparison to those after 36 weeks (22.0±7.8 weeks vs 26.2±5.6, $P=0.01$). There was a positive correlation in-between ($r=0.466$, $P=0.002$). GA at insulin initiation was positively correlated delivery date (before vs after 36 weeks) ($r=0.510$, $P=0.006$). Insulin dosage was negatively correlated with delivery date (final total dosage: $r=-0.453$, $P=0.016$). GA at insulin initiation was negatively correlated with initial basal insulin dose ($r=-0.283$, $P=0.007$). Insulin dosage increased significantly from baseline to final visit (basal: 2.53±2.38 vs 3.73±3.97 U, bolus: 2.27±3.45 vs 5.20±6.12 U, total 4.80±3.88 vs 11.98±12.09 U). A positive correlation was detected between initial and final total insulin dosage ($r=0.643$; $P=0.001$).
Conclusion
Pregnant women need basal insulin more frequently than bolus insulin. Insulin userswith higher hemoglobin A1c level and those who need higher insulin dosage are at higher risk for delivery before 36 weeks. Early insulin initiation avoids delivery before 36 weeks. Basal insulin demand is higher in women who were initiated insulin at an earlier GA.

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Arginine metabolism and gut microbiota changes in pediatric patients with type 1 diabetes

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Introduction
Incidence of type 1 diabetes mellitus (T1DM) is rising steadily around the globe, including Armenia. It is one of the most common autoimmune and metabolic disorders in pediatric population, resulting from autoimmune destruction of pancreatic β-cells leading to insulin deficiency. Gut microbiota

(GM) is reportedly involved in the pathogenesis of T1DM likely by influencing the immune response with the help of arginine-metabolizing enzymes. Arginase is known to contribute to decreased availability of L-Arginine, particularly to nitric oxide synthase, which may cause a subsequent reduction of Nitric oxide synthases/nitric oxide (NOS/NO) production attributed to the pathological processes associated with diabetes. Here, we aimed to investigate the correlation between GM and cytoplasmic and mitochondrial arginase isoforms in peripheral leukocytes of patients with T1DM.
Materials and methods
All T1DM patients ($n=108$) and healthy controls ($n=108$) were recruited at the Muratsan University Hospital, Department of Endocrinology, Yerevan, Armenia. GM was evaluated in the feces of all participants. Qualitative and quantitative examination of the intestinal microflora was performed by sowing fecal samples in appropriate nutritional environments. Fasting peripheral blood was draw into 3.8% sodium citrate anticoagulant, mixed with 6% dextran, and peripheral leukocytes were isolated by conventional procedures. Leukocyte cytoplasmic and mitochondrial fractions were prepared by differential centrifugation. Arginase assay was based on the accumulation of L-ornithine produced by arginase in the reaction mixture during 1 hour incubation and determined by means of ninhydrin. Measurement of the nitric oxide stable metabolites in protein-free samples was performed using Griess-Ilosvay reagent.
Results
In T1DM patients, colony numbersof E. coli ($P<0,001$), Bifidobacterium spp. ($P<0.002$), Lactobacillus spp. ($P<0,0002$) were drastically decreased with a concomitant increase of Candida albicans ($P<0.003$), and a manifestation of Staphilococcus ($P<0.0001$) aureus was also observed. Changes in GM were associated with 1.3 and 1.5 fold increase intheactivity of cytoplasmic and mitochondrial arginase isoforms respectivelyin newly diagnosed T1DM patients, and 1.6 and 1.7 fold increase in patients with duration of T1DM more than 1 year.
Conclusion
Quantitative and qualitative changes in the content of GMin T1DM patients were observed. These were associated with changes in arginine metabolism in peripheral leucocytes. Increase in the activity of arginase isoforms in cytoplasmand mitochondrias of leucocytes in T1DM patients was revealed, associated with a decrease in nitrates level, suggesting the involvement of these processes in pathogenesis of T1DM.

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AEP392

Freestyle libre flash glucose monitoring system in pregnant woman affected by type 1 diabetes: Our experience

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Objective
Prospective observational study in a group of pregnant patients affected by type 1 diabetes (T1DM), that are monitored by the Endocrinology and Pregnancy Unit.
Material and methods
Weevaluated 12 pregnant patients with T1DM in which a FreeStyle Libre Flash Glucose Monitoring Systemwas installed, in addition to their capillary glucose self-control (SMBG), over the past year 2019. Time above range (TAR), time in range (TIR) and time below range (TBR) were measured, and all data captured by the sensor, like daily readings, as well as capillary glycosylated hemoglobin, fetal biometrics and birth data, among others.
Results
The mean age of the patients was 31.58±s.d. 5.48 years. The mean time of evolution of his T1DM was 10.7 years±s.d. 10.31. 75% had not planned their gestation. The treatment in 83% of the patients was basal-bolus therapy and 17% ISCI (Medtronic 640 G). The mean pregestational glycosylated hemoglobin was 7.69%±s.d. 1.73. The mean pre-installation glycosylated hemoglobin was 6.9%±s.d. 0.9. The mean post-installation was 6.2%±s.d. 0.86. Visits were scheduled every 4 weeks. The data covering the 14 days prior to the first medical review since the installation of the sensor were the following: average glucose 128.75±s.d. 27.32 mg. The time above the target (blood glucose >140 mg) was 21.92%±s.d. 22.11, the time on target (70–130 mg) was 57.17%±s.d. 28.29, the time below The target (<70 mg) was 15.08%±s.d. 10.63. The mean low glucose events was 12.14±s.d. 7.64, with an average duration of 125±s.d. 26.65 minutes. The average of data collected by the sensor of the patients was 90.80%±s.d. 9.63, as well as readings of 8.56±s.d. 5.17. Fetal ultrasound was consistent with gestational age in 100% of pregnant women during their follow-up. Childbirth occurred in 50% of patients during the year 2019. The average weight of the newborn was 3191.50±s.d. 136.02 grs.
Conclusions
FreeStyle Libre Flash Glucose Monitoring Systemcan improve the outcome and quality of life in pregnant patients affected byT1DM, however, the evidence to support its use in pregnant women is limited. Studies with more patients are needed to determine if sensor measurements can completely replace theblood glucose self-controls (SMBG).

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2-hr vs 1-hr glucose tolerance testing for pre-DM diagnosis, among HIV-infected patients

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Introduction
Plasma glucose concentration at 1h(1hPG) during an oral glucose tolerance test(OGTT) may be a better predictor of future diabetes mellitus(DM) than 2-h post load glucose concentration(2hPG). HIV-infected individuals may have differential risk of DM compared to the general population, and the optimal diagnosis algorithm for DM in HIV-infected persons remain unclear. We evaluated the agreement of the methods 1 hPG vs 2 hPG) for the diagnosis of pre-DM, as well as the CV risk, insulin resistance and β-cell function in patients with 1 hPG<155 vs≥155 mg/dl.
Methods
As part of a cross-sectional study, 225 Caucasian, non-institutionalized, HIV-1 infected adults under combined antiretroviral therapy (cART) were evaluated. Patients with DM diagnosis were excluded. To define pre-DM with 2 hPG we used 2019 ADA guidelines criteria; to define pre-DM in 1 hPG we used glucose≥155 mg/dl. Differences between groups were tested by unpaired *t*-test. We used HOMA-IR, QUICKIand HOMA-β. Kappa coefficient was used to evaluate the concordance of two methods in pre-DM diagnosis.
Results
We included 225 patients (63.6% males; mean age: 45.3±11.1 years) with baseline BMI: 24.7 (IQR 6.18) kg/m^2, waist circumference 91.0 (IQR 17.9) cm and hip circumference 94.0 (IQR 11.3) cm. The mean fasting plasma glucose (FPG) was: 91.4±11.6 mg/dl, 1 hPG : 158.2±43.4 mg/dl, 2 hPG : 123.1±35.4 mg/dl and A1c:5.2±0.4%. Patients with 1 hPG≥155 mg/dl had higher FPG (95.2 mg/dl vs 87.3 mg/dl; $P<0.001$), 2 hPG(138.9±35.4 vs 105.9±26.3; $P<0.001$), A1c (5.3% vs 5.1%; $P=0.020$) and C-Peptide levels (3.3 ng/ml vs 2.8 ng/ml; $P=0.039$) than those with 1 hPG<155 mg/dl but the difference in HOMA-IR, HOMA-β and QUICKI index between two groups was not significant. Patients with 2 hPG≥140 mg/dl had not only higher FPG levels and at 1hPG, but also higher HOMA-IR (2.9 vs 2.1; $P=0.03$) and C-Peptide levels (3.4 ng/ml vs 2.9 ng/ml; $P=0.027$) than those with 2 hPG<140 mg/dl. 52% of patients had pre-DM diagnosis accordingly 1 hPG criteria and only 27.6% had the same diagnosis with 2 hPG criteria. There was no statistically significant correlation between 1h-OGTTand lipid profile or blood pressure. The concordance correlation coefficient between the methods for diagnosis of pre-DM was 0.363, $P<0.001$.
Conclusion
We observed that, in HIV-infected patients, 1 hPG criteria identified more patients with pre-DM than 2 hPG criteria. Although previous studies, performed in general population, have identified 1 hPG as a method associated not only with decreased insulin sensitivity but also with early signs of cardio-metabolic dysfunction, in our study these differences were not significant between two groups. Further investigation is needed to determine whether 1hPG should be considered as an adjunctive tool to predict dysglycemia and cardiometabolic dysfunction in setting of HIV infection.

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Thiamine-responsive megaloblastic anemia syndrome with dysrhythmia

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Introduction
Thiamine responsive megaloblastic anemia syndrome(TRMA), is an autosomal recessive disorder due to mutation of gene (SLC19A2) encoding thiamine transporter protein TRMA ischaracterized by a triad of anemia, diabetes mellitus, and sensorineural deafness.
Case report
A 15 year old girl admitted to the ERwith diabetic ketoacidosis. She was diagnosed as neonatal diabetesat the age of 16 months and wasput on insulin therapy. Her parents arehealthyfirst cousins. Heryounger sister was deaf, diabetic, died at age of 18 month. At the age to 2 monthsHer mother noticed her child dyspneic with rapidheart beats. Upon medical consultation she was diagnosed as having severe anemia (Hemoglobin: 3 g/dl). Where shereceived blood transfusion. The attacks were recurrent & bone marrow examination was done by the age of 2 revealing; megaloblastic anemia with ringed sideroblasts. She was kept on frequent blood transfusion every 2 weeks. At the age of 9 months, her mother noticed poor response to voices. Audiometry was done showingsensory neural hearing loss and hearing aids were offered . At the age of 2 years, upongradual diminution of vision, electroretinography showed bilateral retinal dystrophy and retinitis pigmentosa. At the age of 9 years, She startedVitamin B1, B6 and B12 Supplementation which markedly reduced the frequency of blood transfusion (1 packed RBCs every 3–4 months). Menarche occurred at the age of 14 years with (Oligomenorrhea)
Physical examination
No dysmorphic features.pulse: 115/minute, pallor. Grade III/VI systolic ejection murmur, over the base.
Laboratory findings
Hemoglobin 7.5 g/dl, MCV 115 fl hematocrit 18%, and white blood cell count 10 000/mm^3 (60% neutrophil, 36% lymphocytes, 4% monocyte). The reticulocyte count; 1% platelet count; 106000/mm^3. The peripheral smear showed anisopoikilocytosis with a predominance of macrocytic cells and no hemolytic findings. Bone marrow aspirate showed normal cellularity but abnormal erythropoiesis with megaloblastic and dyserythropoietic. ECG showed premature atrial extrasystoles with partial RBBB verapamil 40 mg/day was recommended. The patient was put on high dose of oral thiamine (75 mg daily). Hemoglobin showed a steady rise (to Hb=12.8 g/dl) with mild anisocytosis, decreased frequency of transfusion. She was given a hearing aidplanned for cochlear implant.
Conclusion
Children presenting with the triad of anemia, diabetes and deafness should be evaluated for TRMA syndrome, especially in areas with high background consanguinity Stressing the need toward early diagnosis and treatment with thiamine.

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AEP395

Betamethasone administration in pregnant women with pre-existing diabetes mellitus

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Introduction
Betamethasone (BM) is widely used in pregnancy. Its diabetogenic potential is known, and in combination with placental insulin resistance in pregnancy, leads to a transient increase in glycemia. Our aim was to study the changes in glycemia in women with singleton pregnancies and pre-existing diabetes mellitus, under insulin therapy, after administration of BM for obstetric causes.
Materials and methods
We closely monitored and assessed the glycemic profile of 11 women with singleton pregnancies (mean age± s.d.: 35.5±5.0 years; mean gestational age± s.d.: 33.6±3.7 weeks; mean weight gain± s.d. : 9.8±5.6 kg) who were given BM during their hospitalization for obstetric causes. Three women had DM type 1, five women DM type 2, one woman MODY-1, and one woman had cystic fibrosis-related diabetes. Nine women received 24 mg of BM and 2 women 12 mgof BM, respectively. Five women had concurrent thyroid disease. The evaluation of glycemia was based on ten capillary plasma blood glucose measurements/day with point-of-caredevices. The intervention for correction of hyperglycemia was in accordance with ADA and EASD guidelines. We used analysis of covariance to assess the total daily insulin dose after BM, with age, gestational age, weight change in pregnancy, BM dosage, insulin dosage before BM, duration of hyperglycemia as variables and the presence of thyroid disease as a factor.
Results
Asignificant change in the glycemic profile in most patients was noted during the first 24 hours of BM administration, lasting on average approximately 2.1±1.0 days. The mean increase in total daily dose of insulin was of 14.4% (in two women their insulin needs decreased whereas in nine women their insulin needs increased by 25.7%). The noted increase in insulin needs tended to be associated with insulin dosage before BM ($P=0.062$) and the duration of hyperglycemia ($P=0.077$); it was unrelated to diabetes type ($P=0.151$).
Conclusions
The alteration in glycemia, after BM administration was as expected. However, the increase in insulin needs was lower than the reported in the literature increase of 30–40%. This could be attributed to greater attention and compliance of women with previous known diabetes entering pregnancy, compared to women with newly diagnosed diabetes during gestation. Further studies are needed to draw more reliable conclusions.

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AEP396

Falling insulin requirements in women with pregestational diabetes

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Background
Previous studies evaluating the association between falling insulin requirements (FIR) during late pregnancy and adverse maternal and neonatal outcomes yielded controversial results.
Methods
We conducted a retrospective cohort analysis of data collected from women delivering at Shamir Medical Center (a referral university-affiliated facility in central Israel), between 2008–2018. The percent of FIR was calculated by dividing the remainder between the peak total insulin dose during the third trimester and the trough total insulin dose following that peak dose by the highest insulin dose. We compared women with FIR <15% to those with FIR >15% in regard with a composite outcome of any of the following maternal or neonatal complications: Cesarean-section due to fetal distress, pre-eclampsia, induction of labor due to intra-uterine-growth-retardation, small-for-gestational-age or fetal acidemia (cord blood PH <7.2).
Results
In the final analysis, we included 87 pregnancies in 80 women. Sixteen (18.4%) women had a more than 15% FIR during the 3rd trimester. There were 27 women (31%) who had T1DM and the rest T2DM. Women with FIR >15% had lower pre-gestational body mass index (BMI) at baseline (24.9±4.43 vs 28.16±5.79 kg/m^2 $P=0.049$). Women having >15% FIR also had significantly more hypoglycemic episodes during pregnancy though there were no differences in severe hypoglycemia. Composite outcome occurred in 5 (31.3%) deliveries in women with FIR >15% and in 29 (40%) of deliveries in women with FIR <15% $P=0.47$. There were no significant differences in all other maternal or neonatal outcomes in women with FIR ≥15% compared with FIR <15%.
Conclusions
FIR during the 3rd trimester occurs in a considerable number of diabetic women. In our cohort of women with pregestational diabetes (T1DM and T2DM), 3rd trimester FIR was associated with increased risk for maternal hypoglycemia during pregnancy but not with other adverse maternal or neonatal outcomes.

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Exposure to phenolic compounds (Bisphenol A and Methyl Paraben) in pregnancy and its relationship with gestational diabetes mellitus, insulin homeostasis and pancreatic beta cell function

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Objectives
The effect of exposure to endocrine disruptors (exogenous chemical compounds that interfere with hormonal homeostasis), such as Bisphenol A (BPA) and Methyl Paraben (MPB), on gestational diabetes mellitus (GDM) has only been investigated in a small number of studies, with inconclusive results. Our objective was to investigate the association between concentrations of BPA and MPB in urine and the presence of DMG, insulin sensitivity and function of beta cells in a cohort of pregnant women in the Mediterranean area.
Material and methods
Multicenter case-control study, nested in a gestational cohort. Sequential sampling of women with pathological O'Sullivan (week 24–27 gestation), and indication of GDM confirmation test (OGTT 100 g, 3 h) was performed. We analyzed the presence of GDM (Carpenter and Coustan), insulin sensitivity through Matsuda-SOG Index (WBSII), and beta cell function by a trapezoidal model with calculation of the incremental area of insulin and glucose under the curve (AUCins and AUGglu, respectively), and by disposition index (DI) [(AUCins / AUGglu) * WBSII]. Concomitantly, urine concentrations of BPA and MPB were quantified by liquid chromatography coupled to mass spectrometry (HPLC-MS). The relationship between the urinary levels of BPA and MPB with the dependent variables was studied using Spearman correlation tests and multivariate logistic and linear regression models.
Results
Of the 110 women included 34.5 [29–38] years old, 26 [24.7–28] weeks of gestation, BMI 27.9 [24–32] kg/m^2, 40.4% of them met the GDM criteria. The study population had a urinary concentrations of BPA 2.95 [1.17–4] µg/l, and MPB 12.1 [4.4–35.4] µg/l. BPA levels of the 3rd vs 1st tertile were not associated with an increased risk of GDM [OR 0.84 (0.3–2.3)], neither with differences in WBSII or DI. These variables were also not correlated by Spearman. 3rd vs MPB levels 1st tertile were not associated with an increased risk of GDM [0.76 (0.3–1.9)], but with a higher WBSII ($P<0.01$). A negative correlation was also found between MPB and HbA1c, HOMA-IR, AUCins / AUGglu and positive with WBSII ($P<0.05$). This relationship disappears when a multivariate linear regression analysis is performed, in which it is found that BMI (B = –0.1, $P=0.002$) would be the only independent factor associated with WBSII.
Conclusions
In pregnant women with pathological O'Sullivan, higher concentrations of BPA or MPB in urine were not associated with an increased risk of GDM, lower insulin sensitivity, or lower beta cell function.

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AEP398

The prophylactic effects of metoprolol, diltiazem and pilocarpine on hypoglycemia-induced prolongation of QT interval

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Background
Insulin-induced hypoglycemia has been demonstrated to prolong the corrected QT (QTc) interval. Prolongation of QTc interval, especially in diabetic patients using insulin, can cause fatal ventricular arrhythmias. The aim of this study was to evaluate the effects of metoprolol, diltiazem and pilocarpine on hypoglycemia-induced QTc prolongation.
Methods
Thirty rats were randomly distributed into the following five groups: Group 1 (1 ml/kg saline, $n=6$), Group 2 (40 U/kg crystalline insulin + saline, $n=6$), Group 3 (40 U/kg crystalline insulin + 1 mg/kg metoprolol, $n=6$), Group 4 (40 U/kg crystalline insulin + 0.8 mg/kg pilocarpine, $n=6$), Group 5 (40 U/kg crystalline insulin + 2 mg/kg diltiazem, $n=6$). Three hours after insulin injection, blood glucose level was measured in all groups. Blood glucose <40 mg/dl was defined as hypoglycemia. Electrocardiograms (ECG) were taken in lead I (DI) and QTc was calculated by using Bazett' s formula.
Results
Group 2 (insulin + saline) showed that they had significantly prolonged QTc interval compared to control group ($P<0.0001$). However, treatments of the rats with metoprolol, pilocarpine and diltiazem significantly prevented the prolongation of QTc interval compared to insulin + saline group ($P<0.005$, $P<0.005$ and $P<0.01$, respectively).
Conclusion
The findings of the present study demonstrated the efficacy of metoprolol, pilocarpine and diltiazem in the prevention of hypoglycemia-induced QTc prolongation. These agents may be considered in the prophylactic therapy of high-risk patients who are using insulin.

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AEP399

Serum vaspin level in patients with diabetes mellitus type 2 as a predictive index of atherosclerosis

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Background
It has been proved that the adipose tissue is an active endocrine organ. It secretes a large number of adipokineswhich are involved in and affect regulation of metabolic process and can influence pathogenesis of atherosclerosis. Vaspin-new representative of adipokineswhich is secreted by adipose tissue and have an insulin-sensitizing properties. Vaspin engagement into atherosclerotic process poorly investigated.
Aim
To establish the value of plasma vaspin level in patients with diabetes mellitus type 2 (DM2) for prediction cardiovascular disease.
Methods
Thirty-one patient (55.1 ± 1.9 years) with DM2 (9.1 ± 2.8 years of duration) who do not have major adverse cardiovascular events were included to the study. The BMI (28.18 ± 0.8 kg/m^2), fasting plasma glucose level (FPG), HbA_1c, total cholesterol (TC), low-density lipoproteins (LDL), triglycerides (TG), C reactive protein (CRP) serum vaspin level and intima media thickness of carotid arteries (IMT CA) by ultrasound were measured. Control group healthy volunteers (54.8 ± 1.1 years) matched for age, gender and BMI.
Results
The study results showed that all patients had an adequate control of DM2 by oral hypoglycemic agents FPG 8.18 ± 0.92 mmol/l; HbA_1c 7.49 ± 0.21%. Dyslipidemia was present TC 6.40 ± 0.63 mmol/l; LDL 3.39 ± 0.52 mmol/l, TG 2.35 ± 0.15 mmol/l and there is no active process of inflammation CRP 1.33 ± 0.12. Serum vaspin level was significantly higher in patients with DM2 than in control group 3.47 ± 0.42 pg/ml vs 2.42 ± 0.19 pg/ml, $P<0.05$). In multivariate analysis after adjusting for atherosclerotic risk factors vaspin had positive correlation with IMT CA 1.02 ± 0.23 mm vs 0.71 ± 0.11 mm ($r=0,37$, $P<0,02$); immunoreactive insulin (0.6 $P<0,001$) FPG (0.62 $P<0,001$), HbA_1c (0.56, $P<0,001$), TG ($r=0,31$, $P<0,04$). No significant correlation was found between vaspin and BMI, TC, LDL, and plaque existence in carotid arteries.
Conclusions
Serum vaspin level was found significantly higher in patients with DM2 and thicker intima media than age-matched healthy subjects with normal IMT. The vaspin level had significant correlation with all known parameters which are involved in and promoted atherogenesis. Therefore, vaspin may have a pleiotropic effects and can be engaged in atherosclerosis development.

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AEP400

Systematic screening reveals large number of undiagnosed and untreated cardiovascular risk factors in adults with prader-willi syndrome

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Introduction
Prader-Willi syndrome (PWS) is a complex hypothalamic disorder, combining hypotonia, intellectual disability (ID), pituitary hormone deficiencies and hyperphagia. In PWS, up to 3% of patients die every year. In half of the patients, the cause of death is obesity related and / or of cardiovascular origin. Obesity is caused by hyperphagia combined with a low energy expenditure. Untreated hormone deficiencies like hypogonadism and hypothyroidism can cause low muscle mass and low basal rest metabolism (BRM) leading to this low energy expenditure. Patients with PWS should exercise one hour daily to compensate for their low BRM. However, hormone deficiencies usually cause fatigue, leading to exercise intolerance. Musculoskeletal and / or behavioral problems can also cause reduced physical activity. The subsequent sedentary lifestyle can induce cardiovascular risk factors like hypertension, hypercholesterolemia and diabetes mellitus (DM). Another risk factor often present in PWS is sleep apnea (SA). SA can lead to pulmonary hypertension and further increase in obesity. These health problems often remain unnoticed and untreated, which is partly due to the behavioral phenotype of PWS. However, if left untreated, these risk factors can cause cardiovascular complications leading to hospital admission or even death. To reveal yet undiagnosed health problems, we performed a systematic health screening among adults with PWS.
Methods
We systematically screened 115 adults with PWS (mean age 31.4±12.1 y, mean BMI 31.8±9,5 kg/m^2) for the presence of undiagnosed health problems and cardiovascular risk factors. Based on a medical questionnaire, medical file search, extensive interview, thorough physical examination and biochemical measurements we made an overview of the undiagnosed health problems in adults with PWS. If possible, we performed polygraphy to test for SA.
Results
Undiagnosed health problems (hypertension, DM, hypercholesterolemia, SA, hypothyroidism and hypogonadism) were present in 50% of the patients. 10% had multiple undiagnosed health problems simultaneously. All males and 94% of females had hypogonadism and 15% had hypothyroidism. Hypertension and / or hypercholesterolemia were present in 20% and DM was present in 16%. One-third of patients was not on a diet and 22% exercised less than 30 minutes a day. SA was present in 17 of 26 patients tested.
Conclusion
We detected a striking number of undiagnosed health problems among adults with PWS which, if left untreated, can pose a serious health threat. Systematic screening is needed to detect these problems at an early stage. This will prevent complications and might even reduce mortality in this vulnerable patient population.

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AEP401

The severity of insulin resistance in hypertensive patients depending on triglyceride-glucose index

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Objective
To establish the association of triglyceride-glucose index (TyG) index with metabolic parameters of cardiovascular risk (CVR) in patients with arterial hypertension (AH). We examined 255 patients – 123 women and 132 men aged 45–55 years with AH stage II grade 2which were divided on TyG index into two groups: gr.1 –TyG index<4.81 units (n=134) and TyG index>4.82 units (n=121) – gr.2.
Methods
HOMA-insulin resistance (IR), biochemical blood analysis (lipid metabolism parameters, uric acid (UA)).
Results
Analysis of metabolic differences in patients with AH depending on IR presence for TyG index shows that in the case of decreased tissue sensitivity to insulin, the state of lipid metabolism is deteriorated mainly due to disturbances in the system oflipolisis and lipids containing TG, lipid transport system as evidenced by an increase in TG levels of 2.26 times (P<0.0001) and magnitude of the lipid ratio of TG/HDL 2.88 times (P<0.0001). The retention of TC in peripheral tissues in IR (TyG index>4.82 units) is accompanied by HDL lowering by 16.7% (P<0.0001) and an increase in the lipid ratio of TC/HDL by 33, 7% (P<0.0001). Poor efficiency of the reverse transport of TC system functioning in IR condition is also confirmed by the lipid ratio increase of LDL/HDL by 26.3% (P<0.0008), which indicates the advantage of the TC flow to the peripheral tissues over his withdrawal. The lipid profile in IR differs by an additional 24.8% (P<0.0001) increase of non-HDL-C compared to individuals without IR. In relation to TC (non-HDL/TC), this increase is 18.2% (P=0.02). The average of UA did not exceed normal ranges (0.360 mmol/l) in groups compared to TyG index, but was 10.7% (P=0.005) higher at TyG index>4.82 units.
Conclusions
Association of TyG index in patients with AH with atherogenic dyslipidemia as a CVR factor, is realized due to the lipoprotein lipolysis of TG-containing lipoproteins system and inverse TC transport system disorders. The association of TyG index with hyperglycemia and UA levels disoders is realized through metabolic factors as glucose tolerance disturbance and hyperuricemia.

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AEP402

Fish oil and metformin combination to target dyslipidemia in women with polycystic ovarian syndrome

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Background
Woman with Polycystic Ovarian Syndrome (PCOS) are at risk of developingmetabolic syndrome (MetS), insulin resistance, dyslipidemia, Type 2 Diabetes and Cardiovascular Disease. Atherogenic dyslipidemia occurs in>70% of women with PCOS which includes high fasting plasma TG, LDL-C, non-HDL-C or ApoB, and low HDL-C. In addition to diet and lifestyle as the first-line intervention, metformin is commonly prescribed for impaired glucose sensitivity. However, metformin has limited effects on blood lipids in women with PCOS. Furthermore, treatments for dyslipidemia are limited due to safety in young women of reproductive age. Fish oil (FO) and icosapentyl ethyl supplementation, rich in eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), has been shown to reduce fasting TG, but the effectiveness of FO in combination with metformin is unknown in conditions of the MetS and PCOS. The aim of this pilot study was to determine the effect of FO in combination with Metformin on fasting blood lipids in high-risk women with PCOS.
Methods
Participantswere female, age 18–30 years, diagnosed with PCOS who were recruited from the community and endocrine clinics in Edmonton, as part of a randomized clinical trial (n=30). Participants were randomized into intervention groups including: 1) dietary supplementation with fish oil (FO; containing 2520 mg EPA+1680 mg DHA/d, n=13), 2) fish oil+metformin (FO+Metformin 1500 mg/d, n=7) or 3) metformin alone (n=7) for 12 weeks. Inclusion criteria consisted of PCOS diagnosis using NIH-AEPCOSS criteria, BMI>25 kg/m^2, elevated fasting plasma triglycerides (>150 mg/dl), impaired insulin sensitivity (glucose 100–125 mg/dl) and/or diagnosed with T2D (glucose>126 mg/dl). Statistical analysis was completed via 2-way RM-ANOVA (GraphPad 8.0).
Results
FO+Metformin treatment significantly reduced fasting plasma TG from baseline compared to other treatment groups (Combination 2.45±0.43 vs

1.64±0.25*, Metformin alone 1.7±0.2 vs 1.5±0.22, FO 2.3±0.19 vs 2.2±0.19 mmol/l). Combination treatments had no significant effects on fasting insulin-glucose indices or androgen hormones. However, these treatments tended to reduce LDL-C and non-HDL-C (~10%), as well as blood glucose, fasting insulin (~5%) and HOMA-IR (~7–10%).
Conclusion
These pilot analyses demonstrate that the FO+Metformin combination treatment significantly reduces fasting plasma TG levels compared to metformin or fish oil alone in high-risk women with MetS and PCOS. A longer-term trial with larger cohort is warranted to determine the efficacy of this treatment to improve plasma TG, apoB-lipoprotein remnants and early subclinical atherosclerotic CVD risk in women with PCOS.

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AEP403

Epicardial fat accumulation and coronary artery calcification in non-alcoholic fatty liver disease

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Patients with non-alcoholic fatty liver disease (NAFLD) have a higher prevalence of cardiovascular disease, particularly patients with liver fibrosis. Studies have shown a relationship between epicardial fat/coronary calcium and myocardial ischemia.
Aim
Quantify epicardial fat and coronary calcium assessed by computed tomography (CT) in patients with NAFLD. Additionally, determine whether patients with hepatic fibrosis quantitatively assessed by liver elastography (LE), Fibrosis-4 (FIB-4) Score and NAFLD Fibrosis Score correlate with an increased risk of cardiovascular disease by assessing epicardial fat and coronary calcium volume quantified by CT.
Methods
A retrospective and cross-sectional study was conducted in 81 patients with NAFLD. Patients with other causes of liver disease were excluded. Clinical data, serum markers and imaging studies (CT and LE) were obtained. In LE, the presence of increased liver stiffness was determined if ≥8.2 kPa. On CT, epicardial fat and visceral fat were quantified between –45 to –190 voxels and coronary calcium according to the Agatston method.
Results
The average age was 58.98±10.63 years. 82.72% (67/81) were men, with an average BMI of 30.22±4.83 kg/m^2 and body fat (CUN-BAE) of 33.96±7.56%. A 43.21% (35/81) had hypertension, 53.08% (43/81) dyslipidemia, 17.28% (14/81) OSAS, 17.28% (14/81) hyperuricemia, 35.80% (29/81) had type 2 diabetes, 30.86% (25/81) had prediabetes and 64.19% (52/81) were current or former smokers. A moderate-severe insulin resistance (HOMA-IR of 6.43±2.74) was found. Patients with diabetes had 7.44±7.07 years of evolution with a mean HbA1c of 7.19±0.91%. A 13.58% (11/81) presented increased liver stiffness assessed by LE. On average, the patients presented a liver stiffness (LE) of 6.24±2.94 kPa, coronary calcium of 291.97±484.98 and epicardial fat of 201.98±107.85 cm^3. There was a significant positive correlation between liver stiffness (LE) and epicardial fat (r=0.274; P=0.027), as well as with coronary calcium (r=0.66; P=0.005). Additionally, a positive correlation was found between epicardial and visceral fat (r=0.731; $P\leq$ 0.001). Patients with liver stiffness (LE) had a significantly higher epicardial fat volume (283.74±130.11 vs 166.14±81.26 cm^3; P=0.014) and a non-significant higher coronary calcium score (325.13±417.96 vs 124.78±179.93; P=0.188). No significant correlation was found between FIB-4 Score or NAFLD Fibrosis Score and epicardial fat volume or coronary calcium.
Conclusions
Hepatic fibrosis assessed by LE and visceral fat assessed by CT is positively correlated with epicardial fat and coronary calcium. The early identification of these situations may alert clinicians to establish preventive measures in order to reduce the cardiovascular risk of these patients.

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AEP404

Effects of azilsartan vs telmisartan on insulin resistance and metabolic biomarkers in patients of essential hypertension associated with type 2 diabetes mellitus: An open-label, randomized clinical trial

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Background
Based on various preclinical studies, it is anticipated that azilsartan, an angiotensin II receptor blocker, will increase insulin sensitivity in addition to its antihypertensive effect. The present study was undertaken to evaluate the effect of azilsartan compared to telmisartan on insulin sensitivity in patients of hypertension coexisted with type 2 diabetes mellitus.
Methods
This study was a prospective, randomized, active controlled, open-label, parallel-group trial conducted in a single tertiary care center. Participants with grade I or II essential hypertension associated with type 2 diabetes were randomized into two groups. One group received oral telmisartan 40 mg/day and other group receive oral azilsartan 40 mg/day for 12 weeks. The primary endpoint of our study was the change in the homeostasis model assessment-insulin resistance (HOMA-IR) and secondary end points were change in the metabolic biomarkers like leptin and adiponectin values from the baseline at the end of the treatment period. We also evaluated its safety and efficacy on blood pressure.
Result
The mean changes in HOMA-IR from the baseline at the end of treatment were 0.32 (–0.61.1.26) in the telmisartan group and 0.15 (–0.64.0.94.52) in the azilsartan group. The mean difference in the changes from the baseline in HOMA-R between the azilsartan and telmisartan groups was 0.3 (–0.87.1.48) which was not statistically significant. There were also no statistically significant changes observed between two groups in metabolic biomarkers like leptin and adiponectin. Reduction in clinic systolic and diastolic blood pressure were observed at the end of 12 weeks treatment in both groups. No serious treatment-emergent adverse events (TEAEs) were observed.
Conclusion
Both telmisartan (40 mg) and azilsartan (40 mg) didn't show any significant effects on insulin resistance parameters and metabolic markers after 12 weeks administration to patients with grade I or II essential hypertension associated with type 2 diabetes mellitus.

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AEP405

Aldo-keto reductase (AKR) 1C1 – a potential driver of cell cycle progression in hepatocellular carcinoma

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The health burden associated with non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of the metabolic syndrome, continues to escalate. Not only is NAFLD associated with significant liver-specific and cardiovascular morbidity and mortality, but patients are at risk of the development of hepatocellular carcinoma (HCC); a malignancy where the incidence continues to rise and there are very limited therapeutic strategies. Aldo-keto reductase 1C1 (AKR1C1) has a fundamental role in steroid hormone and drug metabolism. It has a variety of enzyme activities including converting progesterone to 20α-hydroxyprogesterone. AKR1C1 has been strongly associated with progression of cancers including breast and lung, as well as the development of chemotherapeutic drug resistance. AKR1C1 is most highly expressed in the liver, and yet its role to regulate metabolic and proliferative phenotype in human hepatocytes or hepatoma cell lines has not been explored. We have hypothesised that AKR1C1 activity contributes to enhanced hepatocellular proliferation through dysregulation of cell cycle regulators including the cyclin-dependent kinase (CDK) family that are crucial in driving G1/S transition. CDKs are also a target of the tumour suppressor, p53. We propose that AKR1C1 inhibition might represent a novel approach to the treatment of HCC. AKR1C1 was highly expressed in human liver, hepatocytes and hepatoma cell lines (HepG2 and Huh7). Functional activity in hepatoma cell lines was confirmed through

the conversion of progesterone to pregnanediol-3-glucuronide, as measured by a commercially available ELISA. Cells were treated with the AKR1C1 inhibitor, 3-Bromo-5-phenylsalicylic acid (5-PBSA) (24 h, 100 μM), which successfully decreased enzyme activity (vehicle: 3.51 ± 1.08 vs 5-PBSA: 0.01 ± 0.01 ng/ml). In HepG2 and Huh7, AKR1C1 inhibition with 5-PBSA down-regulated the mRNA expression of multiple CDKs including CDK1, CDK2, CDK4and CDK6, as measured by real-time PCR. In addition, the cell division cycle 6 gene (CDC6), which encodes a protein crucial for DNA replication, was decreased following AKR1C1 inhibition. We have demonstrated the expression and functional activity of AKR1C1 in human hepatoma cell models. Inhibition with 5-PBSA had a profound impact to alter the expression of crucial cell cycle regulating genes, raising the possibility that AKR1C1 inhibition may represent an emerging strategy to treat HCC.

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AEP406

Connection of glucose control with the 25-OH vitamin D status in type 1 diabetic young patients

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Background and aims
A growing number of studies show the impact of vitamin D deficiency on chronic diseases, such as obesity, type 2 diabetes, cardiovascular disorders etc. Recently the lower limit of vitamin D sufficiency, appeared to be safe and sufficient for skeletal health in the healthy general population, was documented as 20 ng/ml (50 nmol/l). The aim of current work is to evaluate whether the 25-OH vitamin D status is associated with the glucose control in type 1 diabetic young patients.
Materials and methods
We have randomly investigated 64 type 1 diabetic patients of 20–35 years of age, with the duration of diabetes > 5 years. This is the age of bone plateau, when the maximal bone mineral density is already achieved, and is relatively stable period for bone metabolism. The male/female ratio of all investigated patients was 1/1.13, mean age was 24.06 ± 1.08. Fasting serum 25-OH vitamin D and HbA1c levels were measured. Anthropometric and anamnestic data was collected. The patients were divided into three groups depending on their 25-OH vitamin D status: < 20 ng/ml, 20–30 ng/ml, and > 30 ng/ml. All analyses were performed using statistical software (IBM SPSS Statistics for Windows, Version 21.0). In all cases values of $P < 0.05$ were considered statistically significant.
Results
39.1% ($n = 25$) of investigated patients found to have vitamin D insufficiency (< 20 ng/ml); 35.9% ($n = 23$) – vitamin D low sufficiency (20–30 ng/ml); and 25% ($n = 16$) – vitamin D sufficiency (> 30 ng/ml). The groups were comparable based on mean age, sex and diabetes duration. No correlation was found between vitamin D and HbA1c absolute levels. But the mean HbA1c in the groups were as follows: 9.96 ± 0.83; 8.26 ± 0.64 and 7.82 ± 0.79, respectively, showing that in the groups with higher 25-OH vitamin D the glucose control was better ($P < 0.05$). No any connection between sex, age, duration of diabetes, weight and vitamin D status in the groups was revealed.
Conclusion
Lower 25-OH vitamin D is associated with the poorer glucose control in type 1 diabetic young patients. The vitamin D threshold levels should be further revised and investigated, particularly considering the presence of chronic diseases, such as type 1 diabetes, which we suppose should be different from the general population threshold.

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AEP407

Microangiopathy and cardiovascular risk in type 2 diabetic population

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Introduction
Type 2 diabetes is a springboard to metabolic and cardiovascular complications. The objective of our work was to investigate the different cardiovascular risk factors in diabetic type 2 population, and study relation between the level of cardiovascular risk and the occurrence of degenerative complications.
Patients and methods
Retrospective study including 149 patients with type 2 diabetes consultant at the Department of Endocrinology at the Charles Nicolle hospital.
Results
Our population showed a mean age of 59.3 ± 10.6 years, sex ratio of 58.3% and an average of 9.61 years of diabetes. The age was a risk factor in 67.79% of the population and family history of cardiovascular disease were present in 6.04%. Smoking was present in 53%, alcoholism in 8.7% and inactivity in 38.2% of the population. 30.87% of patients were on overweight and 33.56% were obese with android obesity in 69.3% and an average waist size of 99.4 cm ± 11.62. We found a low HDL cholesterol, hypertriglyceridemia and high LDL cholesterol in respectively 65.6%, 34.6% and 34.9% of the population. Hypertension was present in 64.4% of the population. For diabetic macrovascular complications (23.9% of the population) we found coronary artery disease (21.4%), a cerebrovascular accident (6.4%), arteritis of the lower limbs (26.8%) and limb amputation (11.4%). Micoangiopathic complications of diabetes were found in 70.4% of the population with retinopathy in 66.6% neuropathy in 43.3% and autonomic neuropathy in 15.4% of the population. Renal failure was present in 34% of the population with a mean creatinine 105.2 umol/l. The overall cardiovascular risk in patients was calculated according to the SCORE tool with a high risk (5% ≤ SCORE < 10%) in 4.7% and a very high risk (score ≥10%) in 95.3% of the population. Among the latter group microangiopathy complications were more frequent with 69.3% against only 28% for the first group.
Conclusion
The presence of cardiovascular risk factors increases the risk of occurrence of degenerative complications of diabetes. This justifies the need for a comprehensive care, targeting both diabetes and other cardiovascular risk factors in order to improve the profile of our diabetic patients.

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AEP408

Prolonged QT interval during diabetic ketoacidosis: A case series

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Introduction
Prolonged QT syndrome is defined as exceeding of the QT interval on the elecrocardiography (ECG) (> 450 ms in men and > 460 ms in women). It is either congenital or secondary to medication, electrolyte disturbances, heart disease. However, prolonged QT due to diabetic ketoacidosis (DKA) was rarely described. In this study, we tested the hypothesis that QTc prolongation occurs during DKA and returns to normal with resolution of ketosis.
Patients and methods
A retrospective study to evaluate the effect of DKA on the QT interval corrected for heart rate. Our patients were followed in the Internal Medicine department of the regional hospital of Ben Arous within 4 years (2016–2019). We performed electrocardiography during DKA and after recovery. We measured QTc as the QT interval divided by the square root of the R-R interval.
Results
Among 112 patients with a prolonged QT interval on the ECG, 22 patients (19.64%) had DKA, including 12 women and 10 men. The mean age was 54 years (20–87 years). Eighteen patients were followed for type 2 diabetes and 4 patients were diagnosed with type 1 diabetes. There was no medical history of cardiac disease. At the ECG, the QT interval was prolonged with a mean duration of 481 ms (451–543 ms). Three patients were treated with furosemide in one patient, Chlorothiazide in one patient and Indapamide in another leading to a prolongation of the QT interval. Associated electrolyte disturbances were found in 3 patients: 2 cases with hypokalemia and another with hypocalcemia. After correction of DKA with insulin and rehydration, ECG control was normal.
Conclusion
The consistent association between various ketotic conditions and prolonged QTc and/or sudden death raises the question of whether ketosis may directly affect cardiac repolarization. Accurate QT measurement is imperative in DKA patients. Identifying associated electrolyte disturbances, drugs that prolong the QT interval can help reduce the risk of torscardiac arrythemia and sudden death in DKA.

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AEP409

Factors associated with good knowledge of foot health in a population of patients with diabetes

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Aims
To assess the knowledge of diabetic patients on the health of their feetand to identify the associated factors with good knowledge, while providing podiatric advice.
Methodology
It was a descriptive and analytical transversal prospective studyabout 100 diabetic patients (44 men, 56 women; age range 29–87 years). They had an evaluation of their knowledge on the diabetic foot, using a pre-established questionnaire as well as a metabolic evaluation.
Results
The mean age was 54±12.9 years, The sex ratio was 0.78. 56% had a secondary or higher education level. Active smoking was 35% common. Diabetes was type 2 in the majority of cases (78%). The average duration of progression of diabetes was 13.62±6.29 years. 78% of the population has been unbalanced. 34% of the population had good knowledge of preventive measures for diabetic foot. Having good knowledge of preventive measures was significantly associated with secondary or higher education ($P=0.005$), female gender ($P=0.026$) and glycemic control ($P=0.043$).
Conclusion
The prevalence of patients with good knowledge of preventive measures for diabetic foot was low in our study and did not exceed one third of the population. Larger studies are essential in order to identify the factors associated with poor podiatric knowledge and podiatric practices, as well as the factors which slow down adherence to preventive measures recommended.

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AEP410

Foot self-care practices of Diabetic patients in Tunisia

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Introduction
Diabetic foot is a major health problem for people with diabetes mellitus. It can cause serious complications leading to lower extremity amputations. Furthermore, foot self-care practice is one of the most important self-management behaviors to prevent the ocurrence of diabetic foot ulcers.
The aim of this study was to identify foot self-care practices among diabetic patients in a Tunisian population.
Methods
A cross-sectional study was conducted over a period of 3 months. A self-prepared questionnaire was used to collect data from a sample size of 150 diabetic patients at Tahar Sfar hospital and Ezzahra primary care center in Mahdia
Results
The mean age of patients was 56.91±12.6 years with a range of 20 to 86 years. A low level of education was found in 76% of cases. In addition to diabetes, 41.4% of patients had a history of hypertension and 46% of them had hypercholesterolemia. Smoking was found in 13.3% of cases. Half of patients were using oral medications, 28% were using insulin therapy and 21.3% were using both oral and insulin therapies. Regarding patients' knowledge of the diabetic foot, 74.7% had no idea about the impact of diabetes on the foot. Many errors in daily care practices were revealed.
Conclusion
Our patients have a low level of knowledge and a lack of education on diabetic foot. It is therefore important to educate them to prevent serious complications of the diabetic foot.

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AEP411

Particularities of the evolution of type 1 diabetes in 102 Tunisian adolescents

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Introduction
One of the most common chronic diseases in adolescents is type 1 diabetes (T1D).
This period of growth is characterized by hormonal fluctuations and psychological changes which are risk factors for diabetes imbalance.
Aims
Describe the clinical, paraclinical and therapeutic profile in adolescents with type 1 diabetes in Tunisia
Methods
Cross-sectional study conducted atthe Institute of Nutrition in Tunis over a one-year period between January 2017 and January 2018. We have included 102 adolescents with type 1 diabetes (T1D) hospitalized ($n=68$) or followed at the consultation of diabetology ($n=34$).
Results
The population studied consisted of 102 adolescents with type 1 diabetes, 51% of whom were female with an average age of 16.8±1.7 years.
Participants classified underweight (UW) were 3(2.9%), those of normal weight (NW) were 82 (80.4%), overweight (OW) 10 (9.8%) and obese (O)7 (6.9%). Abdominal obesity was present in 21.6% of patients with a significant female predominance (34.6% of girls vs 8% of boys, $P<10–3$). The mean duration of diabetes was 7.1±4.3 years. The mean age of diabetes discovery was 9.7±4.4 years. More than half (53.9%) used human insulin and 46.1% used insulin analog. The daily average of insulin dose was 1±0.4 u/kg/day. Low adherence to treatment was observed in 29.4% of patients. Insulin omission was found in 7.8%. The average fasting glucose was 13±6.1 mmol/l. The average rate of HbA1c was 10.6±2.2% with extremes ranging from 5.8 to 16.8%. The majority (78.9%) of our patients had an HbA1c level>9%. Diabetic retinopathy was noted in 3.9% of patients, peripheral neuropathy in 5.9%, and diabetic nephropathy in 5.9%. Dyslipidemia was diagnosed in 30.4% of diabetics with a significantly higher frequency in girls (girls: 38.5% vs boys: 22%; $P=0.05$).
Conclusion
Diabetes in adolescence is characterized by poor and unstable blood sugar. Improving the quality of care for young diabetics insisting on therapeutic and nutritional education is necessary in order to avoid chronic complications of diabetes and provide them with a better quality of life.

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AEP412

Relationship between chronic pancreatitis and non-alcoholic fatty liver disease in patients with type 2 DM

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Background
People with type 2 Diabetes Mellitus (DM2) more predisposed to Non-Alcoholic Fatty Liver Disease (NAFLD). Accompanied chronic pancreatitis impaired glycemic control by affecting gastrointestinal absorption, also by affecting of pancreatic insulin secretion. We study the frequency of NAFLD in DM2 patients with accompanied chronic pancreatitis.
Material and methods
In 44 people with DM2 blood glucose, HbA1c, Cholesterol, triglycerides, LDLP, HDLP, fibrinogen, ALAT, ACAT, bilirubin levels, prothrombin index, serum alpha amylase activity were measured. In addition pancreas, liver structure assessed by ultrasound. Results showed that 37% observed people with DM2 have NAFLD. Blood glycemia, HbA1c, fibrinogen, ALAT, ASAT, bilirubin levels were comparable in both with NAFLD and without. Blood Cholesterol, Triglycerides, VLDLP levels were significantly higher in patients with NAFLD which confirmed by ultrasound. Interestingly, that 26 (59%) patients with DM2 have accompanied chronic pancreatitis, which determined in 15 patients (94%) in the group with NAFLD and in 11 patients

(39%) without NAFLD, which suggested about involvement of chronic pancreatitis into pathogenesis of NAFLD.
Conclusion
NAFLD is a frequent among people with DM2 and determined in 37%. Interestingly, NAFLD showed the relationship with presence of chronic pancreatitis in people with DM2. Chronic pancreatitis in patients with DM2 involved into pathogenesis of NAFLD.

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AEP413

Fungal necrotizing external otitis in diabetic patients

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Introduction
Fungal necrotizing otitis externa is a serious and potentially life-threatening condition that is challenging to manage. Diabetic patients are susceptible to develop this severe infection. The diagnosis is often delayed and its frequency has increased over the last few years.
Material and methods
we reported 8 cases of fungal necrotizing external otitis in diabetic patients treated in the ENT department of Tahar Sfar Hospital in Tunisia from 1992 to 2018.
Results
Our study investigated three men and five women. They were all diabetics. The mean age was 61 years ranging from 69 to 74 years. All four patients were first treated for bacterial necrotizing otitis externa. Diagnosis was reviewed after a lack of response to antibiotic therapy. Aspergillus flavus was isolated in one case, Candida albicans was isolated in 6 cases an association of candida and aspegillus flavus was found in one case. Computed tomography scan showed signs of invasive necrotizing external otitis in all cases. It showed lysis of the facial canal in one case, sigmoid sinus thrombosis in one case, jugular vein thrombosis in one case and lysis of the carotid canal in one case. One patient developed facial palsy during disease progression. The equilibration of diabetes was obtained in all the cases. Treatment was based on amphotericin B and oral voriconazole during 6 months. Heparin was not used for the cases of septic thrombosis. The side effets of the antifungal treatment are carefully monitoring. After an average follow-up of one year, a regression of the infection was observed in 5 cases, one patient was not followed up, one patient developped a recurrence and one patient died with heart stroke.
Conclusion
Fungal necrotizing otitis externa should be suspected in cases where there is no response to antipseudomonal antibiotic therapy. Deep biopsies from the external auditory canal or the mastoid are usually needed to confirm the diagnosis.

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AEP414

Non-alcoholic fatty liver disease and type 2 diabetes mellitus: Diagnostic methods

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Actuality
Type 2 diabetes mellitus patients have a higher risk of developing severe liver disease compared with non-diabetes patients. According to the data, among patients with type 2 diabetes, the incidence of cardiovascular, cerebrovascular and peripheral vascular diseases, as well as nephropathy and retinopathy, is significantly higher in the case of concomitant NAFLD. The fact of liver damage in T2DM is beyond doubt. The liver plays a key role in all metabolic processes and at the same time is a target in the formation and progression of metabolic disorders, in particular, insulin resistance.
Purpose
To study the feature of the instrumental method for the diagnosis of FibroScan in patients with type 2 diabetes with NAFLD.
Materials and methods
40 patients were examined. 20 patients with type 2 diabetes and NAS and 20 patients type 2 diabetes and NASH. All patients underwent measurements of liver stiffness using a FibroScan. Average age: 56±4.6; Hb1c-9.5%; BMI-30.2 kg/m^2; Diabetes experience 7±2.3 years.
Results
In patients with type 2 diabetes and NAS, F0 was more often detected 42%, and in patients with type 2 diabetes and NASH, F1 was detected 29%. According to the results of FibroScan, the degree of F4 fibrosis was more common in patients with type 2 diabetes and NASH 11%, respectively 4%. The average value of steatosis in 40 patients was: S0-1-2 (5%), S2 – 33 (82.5%), S3-5 (13.5%).

The stage of fibrosis (kPa)	T2DM + NAS *n* = 20	T2DM + NASH *n* = 20
F0	42%	21%
F1	29%	29%
F2	17%	16%
F3	8%	23%
F4	4%	11%

Conclusion
According to our study, fibrotic changes were more common in patients with type 2 diabetes and NASH. Liver FibroScan is an effective approach for the diagnosis of liver fibrosis in patients with type 2 diabetes and NAFLD

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AEP415

Association between diabetic peripheral neuropathy (DPN) and hypertiglyceridemia in patients with type 2 diabetes in georgia

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Background
Diabetic neuropathy is a widespread chronic diabetes complication. This heterogeneous group of conditions affects different parts of nervous system and presents with diverse clinical manifestations. Diabetic peripheral neuropathy (DPN) is a common complication of type 2 diabetes (T2DM), it may cause foot ulcer, gangrene or amputation. The risk of developing DPNincreases with age, diabetes duration and poor glycemia control. About 60% to 70% of all T2DM people will eventually develop DPN. Hypertiglyceridemia is a typical lipid disorder in patients with poorly controlled T2DM.
The Aim of this study was to assesseffect of hypertiglyceridemia on DPN in patient with T2DM.
Methods
In total, 62 T2DM patients with DPN(33 men and 29 women) were enrolled in the Study Group (SG). Their mean age was 56±7 yrs and diabetes durationvaried from 5 to 10 yrs. In all SG patients hypertiglyceridemia was diagnosed. Anotherage, sex and diabetes duration matched 50 patients with normal triglycerides (TG) who had no DPN were used as controls (CG). HbA1c in SG was 8.1±1.2% and inCG – 7.7±1.1%. According to current Guidelines, to assess DPN following neuropathy tests were performed in all the patients: 10-g monofilament test, tip-term/temperature test, vibration test with 128-Hz tuning fork, prick test and neurological examination with Sudoscan, a non–invasive method forassessment of small fiber function (Impeto Medical, France). Results of all neurological tests in SG patients (monofilament, tip-term/temperature, prick, vibration tests) were positive, Sudoscan examination revealed presence of small fiber neuropathy. In CG patients all tests, except Sudoscan, were negative, while Sudoscan revealed small fiber damage. Association between hypertiglyceridemia and DPN was assessed. Serum triglyceride levels in SG patients were elevated (mean TG level 299±45 mg/dl, while in CG patients they were100±20 mg/dl).
Results
According to neurological examinations prevalence of DPN in SG comprised 64, 5% (40 cases). TG concentration was significantly higherin T2DM patients with DPN when compared to patients without DPN and normal TG levels ($P = 0.005$). Elevated serum triglyceride levels were associated with DPN ($P < 0.044$).

Conclusion
This study shows that increased serum triglyceride levelsmay play important clinical role in DPN development in patients with T2DM. The problem needs further investigation with the inclusion of other important parameters.

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AEP416

Hypoglycaemia during ramadan in patients with diabetes from Tunisia

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Introduction
Fasting during Ramadan is an obligatory practice for adultMuslims. Although exemptions exist in certain conditions, including diabetes, the majority ofdiabetic patients fast despite this concession with the risk of complications mainly hypoglycemic accidents.
The aim of this study is to establish the relationship between hypoglycemic accidents and drug treatment, therapeutic education, clinical and biological characteristics oftunisian diabetic patientsduring Ramadan 2019.
Methods
A prospective descriptive observational study including 85 diabetic patients followed at the National Nutrition Institute of Tunis. Clinical and biological data are noted before four to eight weeks and after the month of Ramadan 2019.
Results
The mean age was 55.8 ± 12.7 years. Most of the patients had type 2 diabetes (97.7%). A slight female predominance was noted (52.3%). The average duration of diabetes was 10.6 ± 6.6 years. Two thirds of the patients are classified as high or very high risk for fasting. Only 30% of the patients were allowed to fast. Treatment with oral antidiabetics, insulin, or a combination of the two was prescribed in 50%, 12.8% and 37.2% of cases. The average of HB1AC before and after Ramadan was 8 ± 1.2%, and 8.6 ± 1.35% respectively. Severe hyperglycaemia (>3 g/l) was reported in 5.8% of cases. Hypoglycemic accidents were noted in 18.6% of patients, 14.9% of whom were on insulin ($P = 0.026$), either alone or in combination with oral antidiabetics, 16.27% were at high or very high risk ($P = 0.128$), 87.5% with type 2 diabetics ($P = 0.03$) and 13.95% uneducated for fasting ($P = 0.82$). Most of patients fasted all month (72.1%). Hypoglycemic accidents were the main cause of breaking fasting (62% of cases, $P < 0.01$). Half of the patients did not glycemic monitoring during the fasting but without significant impact on the incidence of hypoglycaemia. In addition, there were no hospitalized patients during this month.
Conclusions
The consequences of fasting in diabetic patients were mainly hypoglycaemia. Insulin therapy wasa predictor of hypoglycemia during Ramadan. Identification of individuals who required Ramadan specific education is essentielto prevent these complications.

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AEP417

Clinical and metabolic impact of ramadan fasting in tunisian patients with diabetes

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Introduction
Ramadan fasting is one of the sacred rites in Islam. Diabetes patients are spared this obligation. However, mostof them insists on fasting.
The aim of this study is to assess the clinical and metabolic impact of Ramadan fasting in Tunisia patients with diabetes during Ramadan 2019.
Materials and methods
Prospective descriptivestudy carried out during Ramadan 2019 including 86 diabetic patients followed at the National Institute of nutrition of Tunis. Clinical and metabolic data were recordedfrom patients' files, as well as by conducting individual interviews and physical exam. The period of our study covered one to three months before Ramadan and one month after it.
Results
The mean age was 55.8 ± 12.7 (23–80 years). The sex ratio was 1,08 (F/M). The average BMI was 28.22 ± 4.22 kg/m^2. Most of patients had type 2 diabetes (97.7%). The average duration of diabetes was 10.6 ± 6.6 years. Patients were treated with oral anti-diabetics alone, insulin or the association between the two, in 50%, 13% and 37% of cases respectively. Two thirds of patients were classified as high to very high risk for fasting and 32.3% had a low or intermediate risk. Only 30% were educated, 24% before one month, 4% before two months and 2% before three months. Half ofof participants (55%) experienced a weight loss after Ramadan, 28% a weight gain, and 18% no change in weight. Furthermore, we did not objectify a relationship between the change in BMI and initial BMI. Regarding the metabolic impact, we noted a significant increase in mean HbA1c (8 ± 1.2 vs 8.7 ± 1.35; $P < 0.01$), but not significant in Triglycerides and glomerular filtration rate while we noticed a non-significant decrease in total cholesterol, LDL cholesterol, HDL cholesterol and uric acid. We did not notice a significant difference inthe parameters studied between educated and uneducated patients. The main complications were hypoglycaemia (18,65%) and hyperglycaemia (5.8%). Otherwise, No acute metabolic accident or hospitalization were reported.
Conclusions
Ramadan fasting had a negative impact on glycemic balance, and a variable effect on the lipid profile and weight status. This underlines the importance ofimprovingthe education of patients with diabetes to avoid acute complications during this month.

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AEP418

Cognitive impairment in patients with type 2 diabetes is associated with increased level of circulating Granzyme B

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Introduction
Diabetes mellitus is known as a factor of cognitive impairment. The risk of dementia in patients with type 2 diabetes mellitus (T2DM) increases almost twice. The results of epidemiological, visualization and autopsy studies showed the presence of both cerebrovascular and neurodegenerative mechanisms of brain lesions. Cell death of key substrates – neurons and endothelial cells lays in the basis of the formation of cerebral disorders. Granzyme B (GrB) is a serine protease, which exerts both intracellular apoptotic and extracellular functions, leading to tissue injury, inflammation and repair.
The aim of the study was to find out role of the granzyme-induced mechanisms of programmed cell death in the development of cognitive impairment in patients with type 2 diabetes.
Material and methods
70 patients with cognitive impairmentin T2DM and 26 healthy individuals who formedthe control group were examined. Patients were classified using neuropsychological assessment tests. The Mini-mental State Examination test (MMSE), Montreal Cognitive Assessment (MoCA) test and the determination of cognitive-induced potentials were used to evaluate cognitive functions. Serum Granzyme B (GrB) was measured by Human Granzyme B Elisa kit (Bender MedSystems).
Results
Mild cognitive impairment was diagnosed in 47 patients with T2DM, dementia in 23 subjects. T2DM patients had 56% higher serum level of GrB than the control group ($P = 0.03$). The changes were statistically insignificant in the group of patients with mild cognitive impairment, while in subjects with dementia the level of GrB was almost twice higher compared to the control group ($P = 0.04$). Positive correlations were established between the MMSE and MoCA tests results of patients with T2DM and levels of GrB, direct correlation – the latent period P300 and levels of GrB ($P < 0.05$). Thus, serine protease GrB can play a role in the mechanisms of brain damage in T2DM by converting procaspase 3 to active caspase 3. Activation of cytotoxic T- cells leads to the release of perforine and granzymes from their granules. Perforine forms in the plasma membrane of target cells the pores through which granzymes penetrate. Also, recent studies have shown that GrB plays an significant role in the processes of destabilization of atherosclerotic plaques, that important in the aspect of vascular dementia in DM.
Conclusion
Cognitive impairment in patients with type 2 diabetes is accompanied by an increase in granzyme-induced apoptotic processes.

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AEP419

Clinical evidence of the cost effectiveness of bariatric surgery in management of type 2 diabetes mellitus and obesity to prevent associated co-morbidity

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Introduction
Diabetes is a chronic condition which has become a major public health concern approaching epidemic proportions globally. Effective diabetes management often presents many challenges. Clinicians and patients often become overwhelmed by the need to address co-morbid chronic conditions in addition to patients' diabetes-specific treatment goals. It is widely accepted that bariatric surgery can help improve health in a range of metabolic diseases, including T2DM and obesity. Bariatric surgeries promote weight loss, which can lead to improvements in hyperglycemia and dyslipidemia.
Case review
A 68year oldwas referred to the to theendocrine team with poor diabetic control, ongoing chronic kidney disease and previous history of non- alcoholic fatty liver and prostate hyperplasia, for which he was taking Metformin- (1 g BD), Forxiga- (10 mg OD), Finasteride- (5 mg OD) and Alfuzosin- (10 mg o.d.). On physical examination the patients Weightwas 131 kg, hisheart rate was – 99 bpm, and hisBlood pressure was 154/8 mmHg. There was no evidence of peripheral neuropathy or ulceration. Laboratory findings showed, *Urea*-8.8, *Creatinine*-114, *eGFR>60* and *HBA1C*-77 mmol/ mol
The patient was referred to a dietician to help with his weight loss and diebetic control. The patient was again seen by the endocrine team 6 months later and his weight remained alarmingly high (126 kg) despite consulting a dietician and his diabetes remained uncontrolled. Following successful gastric bypass surgery in December 2018 the patient lost 20 kg and he showed good diabetic control with glucose level of 4.5–6.0 mmol/l. his most recent HbA1c was 33 which is within normal range.
Discussion
Following, successful gastric bypass the patient glucose level returned to normal physiological level and there was gradually decline in HbA1c. Therefore, all previously prescribed anti diabetic drugs were stopped and the patient also demonstrated substantial weight loss. The use of surgical intervention for obese Type 2 diabetes patients at risk of disease progression should be considered because diabetes is the leading cause of non-traumatic lower extremity amputation and blindness in the United Kingdom. Majority of diabetes-related amputations in England are preventable if patients get the right early preventative care upon recognition of uncontrolled diabetes.
Conclusion
Bariatric surgery is robust means for treating diabetes and obesity. The use of this would limit both the over prescription of anti-diabetic therapy and lower their cost, which at the moment is estimated to cost the NHS over billion pounds.

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AEP420

Pecularities of bile homeostasis in patients with chronic cholecystitis combinedwith diabetes mellitus type 2

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Introduction
In order to improve the early diagnostics of cholelithiasis in patients with chronic acalculous cholecystitis combined with diabetes mellitus type 2 (DM), individual parameters are usually not sufficient. Therefore, we decided to establish and analyze the correlation between the serum and biochemical parameters of bile to evaluate biochemical connections in a system of lipid homeostasis by comorbid pathology. The aim of our study was to determine the peculiarities of disorders of bile homeostasis by patients with chronic acalculous cholecystitis combined with diabetes mellitus type 2.
Methods
A detailed clinical examination was carried out in 50 patients with chronic acalculous cholecystitis combined with diabetes mellitus type 2 (group 1 in the main group), 40 patients with diabetes mellitus type 2 (2 group), 40 patients with chronic acalculous cholecystitis (3 group) and 20 practically healthy individuals.
Results and discussion
In patients of the 1st group, the ratio of bile acids/cholesterol (BA/CH) was significantly lower compared with patients with group 2 ($P<0.05$). It was found that in the patients of the 1st group there was an inverse average strength correlation connection between the serum cholesterol level and the ratio of phospholipids/CH in bile ($r=–0.64$, $P<0.05$). This indicates that the lithogenicity of bile in this category of patients depends on an elevated level of cholesterol in the blood, which can be used as a marker of lithogenesis. Patients in the 2nd group revealed a reliable direct correlation between the level of phospholipids (PL) in serum and the ratio of PL/CH in bile ($r=0.71$, $P<0.05$) and the inverse correlation between the concentration of β-lipoproteins and the ratio of BA/CH in bile ($r=–0.74$, $P<0.05$). In patients of the 3rd group, we found a direct correlation between the level of high density lipoprotein (HDL) in serum and the ratio of PL/CH in the bile ($r=0.76$, $P<0.05$), the level of serum phospholipids andratio of PL/CH in bile ($r=0.66$, $P<0.05$), serum HDL and ratio BA/CH ($r=0.67$, $P<0.05$), and the level ofHDL and the Isaacson index ($r=0.77$, $P<0.05$).
Conclusion
Thus, patients with chronic acalculous cholecystitis and diabetes mellitus type 2 have established a reliable correlations between the serum cholesterol level and the ratio of phospholipids/cholesterol in the bladder portion of the bile in the absence of reliable correlations between the lipids of serum and the bile.

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AEP421

Pecularities of antithyroid autoimmunity indicators in patients with diabetes mellitus type 2 depending on leptin level and impact of selenium-containing medicines intake on their titers

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During the last three decades the number of patients with diabetes mellitus (DM) type 2 have increased, which is associated with an increase in the prevalence of obesity among the world's population. DM type 2 and obesity are closely linked with the production of leptin by adipose tissue. Diseases of the thyroid gland (TG) as well as type 2 DM are the most common endocrine pathologies. Many studies have found an increase of antithyroid antibodies titers against the background of DM type 2. According to the literature data, a chronic autoimmune thyroiditis (AIT) affects 10% of women and 20% of male population.
The aim of the study
To determine the characteristics of antithyroid autoimmunity in patients with type 2 diabetes mellitus, depending on the leptin level in blood serum and develop a method of the identified changes correction.
Materials and methods
Depending on the leptin level in blood serum patients were divided into groups as follows: Group I – level of leptin – less than 10 ng/ml (12 patients), group II – level of leptin within 10–25 ng/ml (19 patients), group III – level of leptin more than 25 ng/ml (15 patients).
Thyroid autoimmunity was diagnosed by antibodies to thyroid peroxidase (AT-TPO) and thyroglobulin (AT-TG) determination in the blood serum.
In order to evaluate the effectiveness of treatment, patients were randomly divided into two groups: 20 people with DM type 2 received standard treatment. The main group included 30 people who receivedsodium selenite, which is equivalent to 100 micrograms of selenium, by 1 tablet per day for 30 days against the background of basic therapy.
Results of the study
According to obtained data AT-TG level in group III was 2.1 times higher than in group I ($P<0.05$). AT-TPO titers in groups II and III was 44.3% and 92.2%, respectively higher than in group I ($P<0.05$).
A significant improvement of indicators that reflect the autoimmune processes against thyroid tissue have been found only in the group of persons who took sodium selenite with standard therapy: the level of AT-TG became 22.3% lower ($P<0.05$) and AT-TPO – 30.6% than before sodium selenite treatment ($P<0.05$)
Conclusions
1. In patients with diabetes mellitus type 2 an antithyroid antibodies titers increase.

2. Significant decrease in antibodies to thyroglobulin and thyroid peroxidase titers in patients with type 2 diabetes mellitus against the background of sodium selenite intake have been observed.

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AEP422

The associations between adipocytokines and future vascular complications in type 2 diabetes

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Aims/Introduction
It is thought that adipocytokines contribute to the increased riskof vascular complications in type 2 diabetes (T2DM). However, some data indicate that adipocytokines may protect against cardiovascular disease. The net effects of adipocytokines on vascular pathology are complex and not completely understood. Although previous our cross-sectional studies showed that adipocytokines such as adiponectin, leptin, and TNF-alfa were associated with vascular complications in patients with T2DM, there is still limited information on the relationship between future development of microangiopathies and adipocytokines in T2DM. The aim of this study was to investigate the relationship between baseline serum levels of adiponectin, leptin, and TNF-alfa and future presence of vascular complications in Korean T2DM.
Methods
Ninety nine patients among 140 patients who were measured baseline serum adiponectin, leptin, and TNF-a levels were recruited. They were evaluated for diabetic nephropathy, retinopathy, neuropathy, and carotid atherosclerosis during follow up.
Results
The mean age and duration of diabetes, and duration of follow up were 53 years, 6.7 years, and 7.8 years, respectively. Baseline mean serum leptin levels were significantly lower in patients with carotid atherosclerosis than in those without it during follow up ($P=0.017$). Multivariate logistic regression analysis showed that the odds ratio for the presence of carotid atherosclerosis in the lowest tertile of leptin was 4.6 (95% confidence interval 1.3–15.7), as compared with the patients in the highest tertile of leptin level. Baseline mean levels of adiponectin and TNF-alfa were not significantly associated with any of the three microangiopathies and carotid atherosclerosis during follow up. Baseline serum leptin levels were not associated with any of the three microangiopathies.
Conclusions
These results suggest that decreased serum leptin levels in T2DM may be associated with future development of carotid atherosclerosis. Future prospective studies with larger numbers of patients are required to establish a direct relationship between plasma adipocytokine concentrations and the development or severity of vascular complications.

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AEP423

Serum osteoprotegerin level in relation to ankle brachial index among type 2 diabetic patients with subclinical hypothyroidism

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Background
Osteoprotegerin (OPG) acts as an important regulatory molecule in vascular disease. The presence of diabetes mellitus greatly increases the risk of peripheral artery disease, Also both subclinical and overt hypothyroidism have been clearly linked with dyslipidemia, which is a known risk factor for peripheral arterial disease.
Aim
We aimed to evaluate the relation between serum osteoprotegerin and peripheral artery disease among type 2 diabetic patients with subclinical hypothyroidism (SCH).
Patients and methods
60 participants were enrolled in the study, (Group1) 20 type 2 diabetic patients with normal thyroid function, (Group 2) 20 type 2 diabetic patients with subclinical hypothyroidism and (Group 3) 20 healthy subjects, they were subjected to complete history taking, complete clinical examination, routine laboratory investigations, serum OPG level, neck ultra sound and Doppler study for ankle brachial index (ABI).
Results
We found that OPG levels were statistically elevated in type 2 diabetic patients with SCH group over type 2 diabetic patients with euthyroidism (*P* value 0.040). Additionally, lower ABI in type 2 diabetic patients with SCH than those with euthyroidism proving increase incidence of PAD in group 2 than group 1 than the nondiabetic patients with statistically significant results in between groups.
Conclusions
Our results found that diabetic patients with SCH revealed an independent association between TSH and serum level of OPG. Likewise we found a statistically significant difference between OPG level and ABI among type 2 diabetic patients. That's why OPG can act as a marker of peripheral artery disease among diabetic patients with SCH.
Keywords: Type 2 DM, sub-clinical hypothyroidism, ankle brachial index, osteoprotegerin.

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AEP424

The role of peripheral serotonin in obese wistar rats studied by using of LP533401

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Background and aims
Although 95% of serotonin is produced in the periphery, its functions have been ignored until now. Recently it became clear that theserotonin system in the periphery regulates multiple physiological aspects independently of the brain-derived serotonin. In particular, peripheral serotonin playsa pivotal function in the regulation of glucose and lipid homeostasis by acting on different organs and cell types. Serotonin produced in pancreatic b- cellspromotes insulin secretion and during pregnancy also b-cell proliferation. Serotonin produced in intestine acts on the liver to promote gluconeogenesis and tosuppress hepatic glucose uptake, and on white adipocytes to promote lipolysis and to suppress glucose uptake, adiponectin production and insulin action. Serotonin produced directly in the adipocytes suppresses thermogenesis and glucose uptake in another functional type of fat – brown adipose tissue. Moreover, serotonin might act directly on muscle to promote glycolysis, and it promotes cytokine production in macrophages. With our study, we want to see how peripheral serotonin affects peripheral insulin resistance and obesity in rats.
Materials and methods
Serotonin is a crucial factor supporting pancreatic b-cell function, using the Tph1 inhibitor – LP533401 (peripheral serotonin inhibitor), in our experiments, aiming suppressing serotonin synthesis in intestinal enterochromaffin cells and in pancreatic b-cells of experimental animals. We used 30 Wistar rats separate in 2 groups- rats with obesityand healthy rats (control group). Each of this groups was separated in other 2 – one with daily intraperitoneal injection of LP533401 (0.2 mg/kg) and one without. In 4 weeks period we were tracking blood glucose level, insulin secretion and rats weight. Thedifferences in the mean values among the groups are greater than would be expected by chance; there is a statistically significant difference ($P\leq0.001$) using SPSS program.
Results
It was shown that after application of LP533401 the weight of the rats in obese groupdecreased by 35.4% ($P<0.05$), and by 15.4% ($P<0.05$) in the control group using LP544401 and no significant dynamic in the groups without daily intraperitoneal injection of LP533401. Theresearch also shows decreasing of insulin resistance by 35.8% ($P<0.05$) in obese rats group using LP533401 compering with the results in the beginning of the study.
Conclusion
Using LP533401 inhibitor for treatment of obesity in male Wistar rats, LP533401 significantly reduces peripheral insulin resistance and further reducing body weight not only in the obese and diabetic rats group, but also in the control group.

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Determining the nutrition, sleep quality and body composition conditions of working shift workers in furniture production

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Approximately 20 percent of the world's working population is working shifts. The shift working system that affects such a large population often causes circadian rhythm disturbances. These disorders adversely affect nutritional habits and quality, sleep patterns and quality, and body composition. The risk of chronic diseases, especially obesity and diabetes, increases due to the direct and indirect effects of disruption in the circadian rhythm. The aim of this study is to compare the data on nutrition habits, sleep quality and body composition of workers working in day and night shifts in furniture production. The study was carried out on a total of 290 male workers working in 6 different furniture manufacturing factories in the 24–60 age range of 215 shifts during the day shift and 75 shifts during the night shift. Demographic characteristics and nutritional habits were questioned by demographic questionnaire. Pittsburgh Sleep Quality Questionnaire was used to determine the sleep quality; In order to determine the dietary quality, a frequency of food consumption questionnaire was used and was evaluated by Mediterranean Diet Compatibilty Score. Body weight, height, waist and hip circumference, body fat percentage and lean tissue mass were measured in order to evaluate the body composition. Results obtained from the study; Significant differences were found between age, body weight, BMI, hip circumference, waist circumference and body fat percentage between shift working status and groups ($P<0.05$). Waist hip ratio and fat free weight did not differ between the groups($P>0.05$). However, it was concluded that all body composition data evaluated were higher in night shift workers. Demographic characteristics revealed that marital status, number of people living in households, education level, alcohol and cigarette smoking, chronic disease, water consumption and occupational accident status were related to shift working status ($P<0.05$). It was found that the mean Mediterranean diet compatibility score ($11,15 \pm 1,93$) of the day shift workers was statistically significant and higher than the mean Mediterranean diet compliance score ($9.35 \pm 1,79$) of the night shift workers ($P<0,05$). When the nutritional habits were examined, it was concluded that shift working status had a significant relationship with the number of meals and skipped meals, but there was no significant relationship between meal preferences. When the sleep quality was examined, it was concluded that other Pittsburgh sleep quality components (subjective sleep quality, sleep latency, habitual sleep activity, sleep disorder, sleep medication use, daytime dysfunction) and total score were significantly higher and higher in the night shift workers ($P<0.05$).

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Effects of bariatric surgery in patients with craniopharyngioma

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Effects of Bariatric Surgery in Patients with Craniopharyngioma
Objectives
The prime objective of this study is the identification of the limiting factors of metabolic surgeries on weight reduction in patients with craniopharyngioma (CP) and consecutive hypothalamic obesity (HO).
Patients
As of now, 37 patients were included, of which5 patients presented with HO and earlier bariatric surgery (mean BMI 50.44 kg/m^2), 5 patients presented with HO without bariatric intervention (mean BMI 43.95 kg/m^2), 9 underwent bariatric surgery as a treatment of alimentary obesity in the past (mean BMI 40.09 kg/m^2), 7 patients were alimentary obese with a mean BMI of 47.33 kg/m^2 and no previous bariatric surgery and 6 participants were healthy controls (mean BMI 24.02 kg/m^2).
Methods
For evaluation of eating behavior and quality of life standardized questionnaires and nutrition reports and for the subjective preference for sweet foods a taste-reward-test were used. A modified oral glucose tolerance test was performed to analyze the gastrointestinal hormone status after a defined test meal. Blood was taken right before and 15, 30, 45, 60, 120 min after meal ingestion.
Results
The BMI of patients with HO and bariatric surgery was significantly higher than that of patients with alimentary obesity and bariatric surgery ($P<=0.05$). Surprisingly, patients with HO that underwent bariatric surgery had still significantly ($P<=0.05$ bzw. 0.01) higher GLP-1 levels than patients of all other groups (at 15 and 30 min after meal ingestion), especially than patients with alimentary obesity and bariatric surgery. There was no statistically significant difference found for PYY.
Conclusion
Patients with HO after bariatric surgery have significantly higher levels of GLP-1 at certain time points after a defined meal, although this doesn't account for PYY. We conclude, that firstly the effects of bariatric surgery are annihilated through the hypothalamic damage and secondly GLP-1 agonists are no valid treatment for most of these patients. Measuring GLP-1 might at least be useful before starting such a treatment.

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Relationship between blastocystis sp. parasitization and metabolic syndrome in an obese spanish population

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Introduction
Blastocystissp. (*BS*) is the most common intestinal parasite that is isolated in human fecal samples. Its pathogenic role is still questioned. While some consider it a beneficial component of the human intestinal microbiota, some evidence relates it with dysbiosis and development of metabolic syndrome (MS). Its presence has been inversely correlated with BMI.
Objective
The objective of this study is two-fold: determining the prevalence of *BS* through molecular analysis fecal samples of Spanish obese subjects and relating it with the presence or absence of MS according to the NCEP ATP III definition.
Methods
Clinical, anthropometric and biochemical data were gathered from type II and type III obese subjects attended in an Obesity Unit in our hospital. Fecal samples were obtained in order to perform PCR amplification and rRNA small subunit sequencing of the *BS* gene. Anthropometric measurements and biochemical analysis were undertaken after an overnight fast. Waist circumference was recorded with a standard flexible non-elastic metric tape.
Results
Fecal samples were obtained from 65 obese subjects of 48.0 (±10.2) years old, 41 women and 24 men. Mean BMI was 45.5 kg/m^2 and every subject showed an abdominal circumference of high risk (130.1±13.6 cm). We obtained PCR positive results for *BS* in 28 samples (43.1%). 46.4% of *BS* positive patients were diagnosed with MS whereas 59.4% of *BS* negative subjects met the same criteria. Attending to individual comorbidities: 51.1% were hypertensive (56.7% in *BS* negative, 42.8% in *BS* positive), 68.0% dyslipidemic (no differences between groups), and 58.2% presented some kind of dysglicemic state (60.1% and 56.7%, respectively) with an incidence of type II DM of 28.5% in *BS* positive patients and 37.8% in *BS* negative patients. No differences were found between groups attending to plasmatic leptin levels (52.3 ng/ml in *BS* positive and 52.4 ng/ml in *BS* negative) or HOMA-R index (6.0 and 6.1, respectively), but higher insulin plasmatic levels (34.7 vs 21.2 mg/ml) were detected in the *BS* negative group.
Conclusions
Yet preliminary, these clinical results suggest a protective effect of *BS* in the development of MS in our population of obese subjects. However, no differences were found in analytical parameters of insulin-resistance, which has been described as the cornerstone of metabolic syndrome.

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Adiponectin and omentin-1 concentrations in patients with systemic sclerosis

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Adipokines belong to a group of proteins involved in the pathogenesis and progression of immune/inflammatory diseases. It is an open question whether and how adipokines contribute to these diseases. Adiponectin might be a key regulator of the immune system, playing a role in the progression of inflammatory disorders. Omentin has been recognized as an anti-inflammatory adipokine with influence on immune response regulation and inflammation, Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by vasculopathy and fibrosis of the skin and internal organs. The studies showed a possible role of adipokines in the development of fibrosis and modulation of the immune response in the course of SSc. We aimed to evaluate plasma levels of adiponectin and omentin-1 in SSc patients in basal conditions as well as in prospective observations.
Material and methods
59 patients with SSc and 27 healthy controls, matched with age, BMI and HOMA-IR, were enrolled in the study. The severity of the skin fibrosis in SSc individuals was evaluated using the Rodnan scale. In all participants, fasting plasma adiponectin and omentin-1 concentrations were assessed using the ELISA.
Results
Omentin-1 levels were significantly higher in patients with SSc compared with the controls. These differences remained marked after adjustment to BMI. No changes were seen between omentin-1 concentrations in prospective analyses in SSc patients (0, 6 months, 9 months). Although adiponectin had a trend to lower values in SSc individuals in comparison to the controls, the differences were not significant. However, after adjustment to BMI, these differences became significant. Similar to omentin-1, there were no adiponectin fluctuations in the follow-up. Amongst two selected adipokines, only adiponectin levels correlated with the Rodnan scale ($R=-0.21$, $P<0.05$). To conclude, adiponectin and omentin-1 cannot be regarded as potential metabolic markers of a course of systemic sclerosis. However, higher omentin-1 and lower adiponectin concentrations after adjustment to BMI, as seen in SSc patients, may indicate an influence of these adipokines on pathomechanisms involved in systemic sclerosis.

Table 1 Basal adiponectin and omentin concentrations in SSc individuals and the controls.

	SSc	Control	P	P (after adjustment to BMI)
Adiponectin (ug/ml)	8.47 ± 4.06	10.6 ± 5.4	ns	< 0.05
Omentin-1 (ng/ml)	604 ± 93	506 ± 138	< 0.05	< 0.05

Table 2 Follow-up assessment of adiponectin and omentin-1 in SSc individuals.

	0	6 months	9 months	p
Adiponectin (mg/ml)	8.47 ± 4.06	8.72 ± 3.85	8.04 ± 3.81	ns
Omentin-1 (ng/ml)	604 ± 193	619 ± 257	601 ± 238	ns

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The management of nonalcoholic fatty liver disease with a choline containing antioxidant compound

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Nonalcoholic fatty liver disease has an increased worldwide prevalence due to obesity and the use of various drugs affecting the liver. The pathogenesis of nonalcoholic fatty liver disease is presently not completely defined. In addition, there is a paucity of agents for its treatment. Choline deficiency has been shown to induce nonalcoholic liver disease. Systemic autoimmune rheumatic diseases require chronic systemic treatment with various agents, which may affect liver function. Therefore, the management of nonalcoholic fatty liver disease attains importance. Prunus mume, the Asian plum of the rosaceae family, has been studied for its antioxidant, anti-inflammatory, and liver protecting properties. The aim was to describe the use of a Prunus mume extract in patients with nonalcoholic fatty liver disease and autoimmune musculoskeletal rheumatic diseases. In a group of 50 patients, 25 male and 25 female, with nonalcoholic fatty liver disease in the context of autoimmune musculoskeletal rheumatic diseases, an extract of Prunus mume 300 mg (Prunus mume extract 150 mg, choline bitartrate 82.5 mg, oleanolic acid 1.3%, ursolic acid 1.7%) was administered once daily. In this group the levels of alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, cholesterol, HDL, LDL and triglycerides were measured before, 1, and 3 months later. Observations were also performed in a control group of 50 patients. A liver ultrasound was performed. In this group of patients with nonalcoholic fatty liver disease in the context of autoimmune musculoskeletal rheumatic diseases after 3 months of treatment with the Prunus mume extract 300 mg daily the levels of alanine aminotransferase decreased significantly by 35.1% ($P<0.01$), those of aspartate aminotransferase decreased by 8.2% ($P<0.01$) and those of gamma-glutamyl transferase decreased by 12.4% ($P<0.01$). The LDL/HDL ratio decreased by 10.9% ($P<0.05$), HDL levels increased by 11.5% ($P<0.05$) and triglycerides decreased significantly by 7.2% ($P<0.05$). The diagnosis of nonalcoholic fatty liver disease in the context of autoimmune musculoskeletal diseases presents a problem andthe systemic treatment of the disorder is presently in the focus of scientific research. The management of nonalcoholic fatty liver disease with a Prunus mume extract has beneficial effects on various metabolic parameters as it has antioxidant, anti-inflammatory and liver protecting properties and may contribute to a good quality of life.

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Muscle endocrinology and its relation with liver disease

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Background
Evidence suggests that muscle mass depletion is associated with poor clinical outcomes in clinical population. However, the significance of sarcopenia in the liver transplantation (LT) population remains unclear. The purpose of this study is to investigate the prevalence and the impact of sarcopenia and sarcopenic obesity in cirrhosis patients awaiting LT.
Methods
We retrospectively analyzed patients who underwent LT at our center between January 2013 to January 2019. Data analysis was performed from October 2019 to December 2019. Body composition parameters including skeletal muscle mass index (SMI) and visceral fat area (VFA) were evaluated by preoperative plain computed tomography imaging at the level of the third lumbar vertebra (L3) and also clinical and biochemical parameters were taken. Sarcopenia was defined using FLEXIT cut-points (SMI: male <50 cm^2/m^2; female <39 cm^2/m^2) and obesity a VFA >130 cm^2. Cox regressions and Kaplan-Meier analysis was performed.

Results
The study included 137 patients (108 men) with a mean age of 57,4 (s.d. 9,05),83 (60,6%) had sarcopenia and 29 (21.2%) had sarcopenic obesity. Multivariate analysis identified low SMI as independent risk factor for death after LT [OR 8,293 (3,284–20,040) $P<0.0001$].
Conclusions
Preoperative sarcopenia is an important independent predictor of post-liver transplantation mortality in cirrhosis patients. A high SMI is an excellent predictor for survival in this group of patients.

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Differential miRNA expression profile in adipose and muscle tissue of obese individuals with T2DM

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Aim
Obesity represents a risk factor for the development of type 2 diabetes mellitus (T2DM). Although, this seems to reflect common environmental and genetic factors underlying both pathologies, the link between these conditions is not so clear. A diverse group of elements, including miRNAs, has been implicated in the development of these two metabolic diseases. miRNAs are involved in complex regulatory networks of gene expression. This suggests that alterations in their expression levels, their cellular location, and their action may have far-reaching effects on cellular physiology and even invoke sustained alterations. Thus, the main objective of this pilot study is to establish if the differential miRNA expression profile in patients diagnosed with obesity are associated with the presence of T2DM.
Materials and methods
miRNA-seq technology (NGS) was applied to sequence the miRNA profile of visceral adipose tissue (VAT) ($n=6$) and paired skeletal muscle tissue (SMT) ($n=6$) of obese women which underwent bariatric surgery, with and without T2DM. To establish the miRNA expression pattern in the different tissues analyzed, miRDeep2 software was used. Differentially expressed miRNAs analyses were performed with edgeR. Prediction of target genes of the miRNAs was established using the TargetScan program. Statistical computing was performed in R environment.
Results
After sequencing was performed, patients with T2DM were compared to those without it. Expression analysis revealed 95 (61 up and 34 downregulated) differentially expressed miRNA out of 807 (11.77%) in VAT and 40 (16 up and 24 downregulated)out of 663 miRNAs (6.03%) in SMT. Besides Principal Analysis Component didn't showed a clear separation between groups. Despite this, GOrilla tool was used to identify the biological processes that could be altered. Biological processes upregulated in the SMT of obese patients with T2DM were involved in cell migration, signal transduction or regulation of metabolic processes. Downregulated pathways were mainly related to negative regulation of transcription mechanisms and macromolecule biosynthesis. Otherwise, biological processes implicated in covalent chromatin modification were upregulated in VAT of T2DM obese individuals. Interestingly, in VAT, downregulated miRNAs identified were significantly enriched in pathways related to glucose response. Some genes that appeared in this last category were: PPARGC1A, PDK3, LIN28A, ACVR1C.
Conclusions
Patients with obesity and T2DM have a differential miRNA profile in those tissues associated with insulin resistance compared to those that are not. Further studies will be necessary to analyse the genes and routes actually involved in the development of T2DM.

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Do early gestation maternal body composition parameters identify neonates born large for gestational age?

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Background
Globally, birth-weights are increasing progressively. Birth-weights large for gestational age (LGA) defined as ≥90th centile are linked to increased delivery complications, and adiposity in the neonate. This has been linked to glucose intolerance and CVD later in life. Oversupply of nutrients *in utero* contribute to excess foetal growth, and maternal obesity may contribute to this rise. The aim of this study is to examine the relationship between parameters of maternal body composition to neonatal birth weight.
Methods
A prospective observational study was undertaken. Pregnant women aged between 18–50 y of age with gestational age between 10–16 weeks were included in the study. Women aged ≤18 y, twin-pregnancies, known foetal anomaly or pre-existing condition affecting oedema status were excluded. 8-point skinfold thickness, MUAC, waist, hip, weight and ultrasound measurements of subcutaneous (SAT) and visceral abdominal adipose (VAT) were measured. Birth outcomes were abstracted from medical notes post-partum. Birth centiles were adjusted for maternal ethnicity, weight, height and gestational age at birth. Shapiro Wilk's test and visual inspection of Q-Q plots were used to assess distribution of data. Spearman rho correlation analysis was used to assess the relationship between all test variables and outcome measures as continuous variables. Non-parametric independent sample test was used to assess differences between group medians using LGA as a binary-classification.
Results
224 women were recruited in their first trimester of pregnancy. Twenty five neonates were born LGA. Very few significant, but weak (rho~.1) correlations were found with unadjusted birth weight and all test variables. No correlations were found for all test variables when correlated with birth weight centile. Medians and 95% confidence intervals.(CI), as well U statistic asymptotic *p*-values are reported for both groups in Table 1 below. No test variables were found to be statistically different ($P<0.05$) between neonates born LGA and non-LGA.

Table 1 Medians (95% CI) for each dependant variable, and asymptotic p value between LGA and non-LGA

	LGA ($n=25$)	Non-LGA ($n=199$)	*P*
BMI	24.9.(23.3–28.6)	25.9.(25.3–27.1)	.979
Weight	65.7.(63.0–78.7)	69.5.(68.3–73.5)	.768
Height	164.3.(162.6–167.2)	165.1.(163.4–165.7)	.936
Ultrasound measures			
Abdominal(SAT)	1.45.(1.27–1.82)	1.37.(1.35–1.58)	.671
Abdominal(VAT)	.78.(.65–1.04)	.84.(.85–1.03)	1.0
Abdominal(Total)	2.37.(1.94–2.83)	2.32.(2.22–2.60)	1.0

Skinfold Thickness			
Bicep	13.6.(12.7–18.8)	14.3.(14.7–17.4)	.689
Tricep	21.4.(20.2–26.2)	21.3.(21.6–24.3)	.852
Subscapular	16.8.(15.2–22.6)	18.3.(19.3–22.9)	.669
Supra-iliac	32.1.(25.7–36.9)	26.2.(26.6–30.6)	.350
Supraspinale	21.4.(16.9–25.8)	17.9.(18.5–22.1)	.173
Abdominal	27.4.(23.0–31.4)	26.2.(25.7–29.4)	.363
Thigh	35.8.(35.7–40.7)	34.2.(31.6–44.4)	.893
Calf	22.2.(17.1–26.2)	19.9.(20.0–23.3)	.611
Total SFT	163.8.(148.4–202.9)	160.7.(163.4–186.1)	.392
Appendicular SFT	95.2.(83.3–114.0)	91.9.(92.5–105.1)	.979
Trunkal SFT	93.8.(82.1–115.3)	86.8.(90.6–104.6)	.979
% body fat	38.1.(36.2–42.3)	38.0.(38.3–40.9)	1.00
Girths MUAC	30.0.(28.4–32.3)	30.2.(29.6–31.2)	.936
MAMC	23.0.(21.8–24.4)	22.7.(22.7–23.7)	.979
Waist	80.2.(78.1–88.3)	80.3.(81.1–85.1)	.957
Hip	94.8.(91.9–104.1)	95.0.(94.7–98.8)	1.000

*=statistically significant at $P \leq 0.05$

Conclusion
Parameters of body composition in early gestation do not predict neonates born large for gestational age.

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Associations between FSH levels and indices of total and regional obesity in women after menopause

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Introduction
Recent evidence reports a controversial extra-gonadal role of follicle stimulating hormone (FSH). Conflicting data support that the association between FSH and obesity might be maintained by a direct or even indirect effect to the adipose tissue. The aim of this study was to evaluate the associations between FSH concentrations and various obesity indices in women after menopause.
Patients and methods
This cross-sectional study included 420 postmenopausal women (age 55.6±6.5 years, 8.01±6.7 years since menopause) with low insulin resistance (inclusion criteria: years since menopause>1, FSH>25 IU/ml, HOMA-IR<5). We recorded anthropometric parameters. Indices of regional adiposity were sonographically assessed, including subcutaneous fat and preperitoneal fat. Blood samples were obtained for biochemical and hormonal evaluation.
Results
Mean values of BMI were 25.8±4.0 kg/m^2. Waist circumference and BMI presented a stepwise decrease with increasing quartiles of FSH (Waist, FSH Q1 vs Q2 vs Q3 vs Q4: 93.2±2.4 vs 87.6±4.4 vs 85.4±1.8 vs 80.89±2.8; BMI, FSH Q1 vs Q2 vs Q3 vs Q4: 27.6±5.2 vs 26±4.8 vs 25.8±7.1 vs 23.9±2.9; ANOVA p-value for linear trend<0.001, both cases). Similarly, subcutaneous and preperitoneal fat measures decreased linearly with increasing quartiles of FSH (ANOVA *P*-value for linear trend<0.001). Stepwise linear regression analysis showed that preperitoneal fat is inversely associated with FSH, independently of circulating estrogen (*b* coefficient=–0.130, *P*-value=0.029) and traditional cardiovascular risk factors. The association between FSH and subcutaneous fat was not evident following adjustment for circulating estrogens, implying a possible mediation effect of the latter on this association.
Conclusions
FSH is inversely associated with indices of total and regional adiposity in women after menopause. The exact mechanism of this interaction remains to be elucidated in future studies.

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AEP434

Thyroid stimulating hormone, insulin resistance and leptin in patients with obesity after bariatric surgery

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Background
The function of the thyroid gland effects on obesity and comorbidities. It has been proven for bariatric surgery to be the most effective in obesity treatment.
Aim
To evaluate the dynamics of body weight, thyroid status, leptin and insulin resistance in obese patients after bariatric surgery.
Materials and methods
78 obese patients were observed after bariatric surgery (sleeve gastrectomy – 46, gastric bypass – 32). Body mass index (BMI), thyroid stimulating hormone (TSH), free T4, fasting plasma leptin, insulin and glucose were estimated; the insulin resistance index HOMA-IR was calculated. The dynamics of body weight was estimated by BMI and the excess BMI loss (% EBMIL). After 3 years of follow-up, 50 patients were examined.
Results
Subclinical hypothyroidism (SH) was detected in 37.2% of patients with high degrees of obesity. A correlation was found between BMI and TSH level (R=0.5; P=0.01). HOMA-IR was increased in most patients with obesity of the II and III degree (5.2±2.3 ng/ml). In the SH group, the leptin level was significantly higher than in the group with a normal TSH level: 44.1±7.4 ng/ml and 33.0±4.7 ng/ml (P=0.004). Among patients with initial SH, spontaneous reduction of TSH levels occurred in 42.7% patients 3 years after surgery.
Conclusions
Postoperatively, the decrease of BMI was associated with the decrease of TSH, leptin and HOMA-IR. The data obtained may reflect the effect of adipose tissue on the functional state of the thyroid gland in patients with high degrees of obesity after bariatric surgery. This seems to be extremely important for maintaining body weight.
Keywords: obesity, thyroid stimulating hormone, leptin, insulin resistance, bariatric surgery.

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AEP435

Fructose-induced alterations of hepatic lipid metabolism are modulated by chronic stress in male rats

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Overconsumption of fructoseenriched beverages and everyday stress are both involved in the pathogenesis of metabolic disorders through their effects on hepatic lipid metabolism. The aim of this study was to investigate whether highfructose diet and chronic stress synergistically perturbs lipid metabolism in rat liver. Therefore, we analyzed the effects of 9-week 20% liquid fructose diet and 4-week chronic unpredictable stress, separately and in combination, on dyslipidemia, VLDL-TG kinetics, intrahepatic triglycerides (IHTG), liver *de novo* palmitate (DNPalm) content and fatty acid (FA) composition. In parallel, hepatic fractional *de novo* lipogenesis (fDNL) by stable isotope tracer protocol, as well as expression of lipid metabolism regulators were also analyzed. Results showed that highfructose diet led to hypertriglyceridemia, increased plasma VLDL-TGs and free FA (FFA), and increased visceral adiposity. Fructose diet also augmented the

level of palmitate, palmitoleate and oleate in the liver, the latter being result of increased desaturase activity. In addition, newly synthesized palmitate (DNPalm content) was increased in the liver of fructose-fed animals, most likely as a result of stimulated fDNL. Chronic stress alone did not exert such effects, but when combined with fructose, stress decreased FFA level, ameliorated fructose-induced TG accumulation, and augmented the release of VLDL-TGs. Stress also enhanced the effects of high-fructose diet on fDNL, which was accompanied with increased expression of key regulators of lipid metabolism, that resulting in stimulated export of newly synthesized palmitate in the form of VLDL-TGs. These results imply that high-fructose diet affects hepatic lipid metabolism by stimulating fDNL and increasing *de novo* synthesized palmitate, which is partially accumulated in the liver and in part released into circulation in the form of VLDL-TGs. On the other hand, stress in combination with high-fructose diet potentiated hepatic fDNL, but it decreased temporary TG storage and redirected newly synthesized palmitate into VLDL-TGs. Thus, the combination of high-fructose diet and chronic stress, as hallmarks of modern lifestyle, exerts more detrimental influence on lipid homeostasis than the individual factors, judged by stimulated fDNL and increased export of VLDL-TGs to non-hepatic tissues.

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AEP436

Autoimmune polyglandular syndrome type ii presenting as an endocrine emergency

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Introduction
Autoimmune polyglandular syndrome (APS) is a group of polyendocrinopathies characterizedby multiple glands insufficiencies associated with other autoimmune diseases resulting from immune mediated destruction. We describe a patient with type 2 APS presenting first with diabetes type 1 followed later by adrenal insufficiency and Hashimoto disease.
Case report
A 23-year-old male, known with diabetes type 1, presented with a very low blood pressure. He complained of nausea, vomiting, general weakness, easy fatigability, postural dizziness and gradual darkening of the skin since 3 months.
Physical examination revealed both general hyperpigmentation and vitiligo. Laboratory studies showed significant hyponatremia, hyperkaliemia. Morning cortisol was very low 28 nmol/l (22.1–353) and elevated ACTH 1557 ng/ml (7.2–63.3), with a high level of adrenal autoantibodies, which confirm the diagnosis of autoimmune primary adrenal insufficiency. He was started on replacement therapy with physiological doses of prednisolone and fludrocortisone resulting in marked improvement in his symptoms. Further evaluation revealed also an auto-immune hypothyroidism which required Levothyroxine supplementation.
The analysis for mutations in the AIRE gene was negative, without excluding genetics polymorphisms. Screening for other auto-immune diseases associated with APS 2 was negative.
Discussion
Both APS 1 and 2 are associated with type 1 diabetes. The type 2 syndrome is much more prevalent than the type I syndrome and primary adrenal insufficiency is its principal manifestation. Adrenal insufficiency is the initial manifestation in about 50 percent of patients, occurs simultaneously with autoimmune thyroid disease or diabetes mellitus in about 20 percent, and follows them in about 30 percent.
Our patient had type 1 diabetes and presented with adrenal insufficiency with an adrenal crisis. He was diagnosed as a case of APS type 2 consistent ofAddison's disease, type 1 diabetes, autoimmune thyroid disease and vitiligo. We could not detect mutations in the AIRE gene. However it is possible that certain mutations are not detectable with the used technique.
Conclusion
In type 1 diabetes patients and their relatives a search for APS is crucial given predilection to other concomitant autoimmune diseases. Furthermore regular surveillance in these patients is crucial to screen for these other autoimmune disorders even decades after the initial diagnosis.

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AEP437

Hepatic steatosis indices as a predictors of vitamin D3 deficiency in patients with non-alcoholic fatty liver disease and type 2 diabetes

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Background
Recently, vitamin D3 deficiency is considered one of the factors associated with the development of non-alcoholic fatty liver disease (NAFLD). The aim was to evaluate steatosis indices and metabolic parameters in NAFLD depending on D3 status.
Materials and methods
According to the recommendations of the European Society of Endocrinology, all patients were divided into 3 groups: group 1 – with an optimal level of vitamin D3 (30 ng/ml); group 2 – D3 insufficiency (21–29 ng/ml) and group 3 – D3 deficiency (<20 ng/ml).
Results
The study included 126 T2D patients with NAFLD diagnosed with US. The highest hepatic steatosis (HSI) and fatty liver (FLI) index values were diagnosed in D_3 deficiency as compared to optimal group (HSI – 43.34±6.59 vs 39.67±4.37; $P=0.032$ and FLI – 79.21±19.61 vs 64.96±17.72; $P=0.007$). Triglyceride and glucose index (TyG) also insignificantly growth parallel to D3 status worsened ($P=0.175$). In multivariate logistic regression analysis according to the results obtained, regardless of the transaminases activity HSI (Nagelkerke $R^2=0.215$) and FLI (Nagelkerke $R^2=0.163$) were associated with vitamin D_3 deficiency. According to other logistic models, HSI and TyG indices (Nagelkerke $R^2=0.358$) as well as body mass index (BMI) and T2D duration (Nagelkerke $R^2=0.328$) were independent predictors associated with D3 deficiency in this cohort of patients.
Conclusions
hepatic steatosis indices (HSI, FLI and TyG) independently from anthropometric parameters and transaminase activity associated with D3 deficiency in NAFLD patients.

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AEP438

Clinical differences between patients with new-onset diabetes and those without it in a cohort of individuals with pancreatic cancer

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Background
Pancreatic Cancer (PC) is uncommon; however, it is one of the most deadly cancer types of all. New-onset diabetes (NOD) is associated with a higher risk of pancreatic cancer than general population, particularly if late-onset. An association between new-onset diabetes and increased mortality in patients with pancreatic cancer has been suggested but clinical relevant differences between those individuals with new-onset diabetes and those without are not well established in this population.
Aims
We aim to identify if any clinical differences between individuals with new-onset diabetes and those without exist within a cohort of patients with pancreatic cancer.
Materials and methods
The data was obtained from an institutional registry of 236 patients with pancreatic cancer at '12 de Octubre' University Hospital in Madrid, Spain during the period of time from 2013 to 2017. The patients' imaging studies and hospital records were reviewed. Diabetes Mellitus (DM) was defined by known medical history, or abnormal fasting blood glucose and HbA1c levels according to the American Diabetes Association 2019 criteria within four years of the cancer diagnosis. New-onset diabetes was defined by an arbitrary duration cutoff of ≤3 years since diagnosis. SPSS25.0 software package was used to perform the statistical analysis.
Results
A total of 222 patients fulfilled the inclusion criteria and were included in the final analysis. Patients were predominantly white (215, 96.8%) males (55%) with a median (Interquartile range, IQR) age of 69 (15) years. The median age of the patients was 69 years; 62 (27.9%) patients were 76 years of age or older and had pathologically confirmed pancreatic cancer. Almost one third of patients (27.3%) presented NOD criteria before PC diagnosis,

it accounted for 31.6% of those with a previous history of diabetes. Before PC diagnosis, Patients with NOD had presented impaired fasting glucose more frequently than those without NOD, they also presented with higher fasting plasma glucose value at diagnosis of PC ($P<0.05$). There were no statistical differences in terms of previous history of alcohol consumption, smoking, body-mass index, hepatitis B or C virus immune status, family history of pancreatic cancer or diabetes, A1c, Ca19.9, Amylase, GOT, Alkaline Phosphatase, or GGTvalues at diagnosis of PC ($P>0.05$). Tumor location, size or stage, presence of metastatic disease, metastatic location or bile duct obstruction did not differ between individuals with NOD and those without NOD ($P>0.05$).

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AEP439

HbA1c in the diagnosis of dysglycemia

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Introduction
Type 2 diabetes is a painless and silent pathology, often overlooked, 30% to 50% underdiagnosed. Its prevalence is constantly increasing. It affects 3 new cases every 10 seconds and more than 6 million per year.
Aim of the work
Compare the HbA1c test to the carbohydrate status established by the HGPO on a sample of an unknown Algerian population with diabetes but at high risk. And try to establish HbA1c thresholds by appreciating the validity of this test for the diagnosis of diabetes mellitus, pre-diabetic states and normal subjects. This test has not yet been validated by Algerian national studies.
Material and method
500 patients over the age of 40, consultants at the level of primary care structures, volunteers, but at high risk of diabetes, are subjected to a questionnaire, then to screening by the realization of oral hyperglycemia (HGPO), an HbA1c (HPLC method), an FNS, and an ophthalmological examination (fundus). The sensitivity and specificity of HbA1c at different thresholds for the diagnosis of diabetes and pre-diabetes were studied by ROC curve.
Results
53.2% of patients have dysglycemia: 23.8% have diabetes mellitus, 29.4% have pre-diabetes: 6.8% moderate fasting hyperglycemia (HMJ). 22.6% ITG glucose intolerance. The optimal HbA1c threshold for the diagnosis of diabetes mellitus is 6.27% with a sensitivity of 78% and a specificity of 88%, VPP: 67.88%, VPN: 92.83%, AUC is 0.919. For the diagnosis of pre-diabetes, the optimal HbA1c threshold is 5.83%, with a sensitivity of 71% and a specificity of 81%, VPP: 80.6%, VPN: 72%. The AUC is 0.8157.
Conclusion
The prevalence of diabetes and pre-diabetes in this work is high (23.8% and 29.4%). The use of HbA1c by a standardized method can be a means of screening in subjects at high risk subjects. This HbA1C screening strategy should be verified at the level of the general Algerian population and involve a periodic assessment.

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AEP440

Diabetic ketoacidosis with hypertriglyceridemia-induced acute pancreatitis as first presentation of diabetes mellitus associated with risperidone treatment, a case report

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The triad of hypertriglyceridemia-induced acute pancreatitis with concurrent diabetic ketoacidosis (DKA) is rare in previously undiagnosed diabetic patients. Drug-induced diabetesis one of the main adverse effects of Risperidone, a second generation (atypical) class of antipsychotic used in the treatment of schizophrenia and bipolar disorder, however, Risperidone-induced diabetic ketoacidosis is rare. We are reporting a case of diabetic ketoacidosis associated with hypertriglyceridemia- induced acute pancreatitis as the first presentation of Risperidone-induced diabetes
Case
A 29 years old Pakistani male with a background diagnosis of schizoaffective disorder presented to the Emergency Department with nausea, vomiting and abdominal pain three weeks after starting Risperidone treatment. He reported a history of polyurea and polydipsia few days after initiation of Risperidone treatment. Examination showed obese male with evidence of dehydration and abdominal tenderness. Laboratory investigations revealed marked hyperglycemia with blood glucose level of 583 mg /dl and high anion gap metabolic acidosis. It also showed evidence of acute pancreatitis with serum lipase more than 15 000 U/l (Normal range 73–393) associated with severe hypertriglyceridemia with triglyceride level more than 2000 mg/dl (Normal range less than 150). He was managed with intravenous insulin infusion and hydration as per diabetic ketoacidosis protocol. He responded slowly and required high doses of insulin to correct his hyperglycemia, metabolic acidosis and hyperglyceridemia. Acute pancreatitis responded well to conservative measures. The patient was discharged on subcutaneous insulin therapy along with oral fenofibrates.
Conclusion
Risperidone induced diabetic ketoacidosis with concurrent hypertriglyceridemia-induced acute pancreatitis is rare. Prompt recognition of the coexistence of these three entities is crucial for adequate management.

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AEP441

Does the association between patterns of fruit and vegetables and metabolic syndrome incidence vary according to lifestyle factors and socioeconomic status?

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Background
The aim of this study was to investigate the association between the identified patterns of fruits and vegetables and metabolic syndrome incidence, and to investigate whether lifestyle factors (weight change and smoking) and socioeconomic status (education and occupation status) modify the effect of the patterns on metabolic syndrome risk.
Methods
We prospectively studied 1915 participants of the Tehran Lipid and Glucose study aged 19–74 years who were follow-up for dietary assessment using a validated, semi-quantitative food frequency questionnaire. Linear regression was used to compute energy-adjusted intakes of fruit and vegetables using residual methods. Patterns of fruit and vegetables, based on 17 food groups, were obtained by factor analysis (principal component analysis). To simplify the interpretation, an orthogonal rotation procedure (varimax rotation) was used. Four interpretable factors were retained based on the Cattel test graph (screen plot). Dietary patterns were describe according to foods with loadings>0.3. Four extracted dietary pattern scores were categorized into tertiles. Additionally, we evaluated the effect modification of lifestyle factors and socioeconomic status on the association between different dietary fruit and vegetable patterns and risk of MetS using Cox regression. A significant interaction was defined as $P<0.20$.
Results
We identified four major patterns of fruits and vegetables by factor analysis: 'fresh fruit pattern', 'vegetable pattern', 'dried Fruit and cruciferous vegetable pattern', 'potatoes and fruit juice pattern'. After control for potential confounders, the highest tertile of 'vegetable pattern' was negatively associated with MetS risk (HR: 0.74, 95% CI : 0.60–0.91) and the highest tertile 'potatoes and fruit juice pattern' increased risk of MetS (HR: 1.49, 95% CI : 1.23–1.82). Among participants with weight gain<7% during follow-up, all four identified patterns reduced Mets risk, compared to the reference. When stratified by smoking, 'vegetable pattern' and 'dried Fruit and cruciferous vegetable pattern' lowered MetS risk among non-smokers. Stratification based on education, resulted in MetS risk reduction across tertiles of 'fresh fruit pattern', 'vegetable pattern' and 'dried Fruit and cruciferous vegetable pattern' in educated participants.
Conclusions
The reduction in metabolic syndrome risk caused by fruits and vegetables intake depends on the modifying effect of lifestyle and socioeconomic factors.
Keywords: metabolic syndrome, fruits, vegetables, lifestyle, socioeconomic status.

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AEP442

Diabetes mellitus and glucose-6-phosphate dehydrogenase deficiency: About a case report

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Introduction
The glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme deficiency in humans. In red blood cells, the pentose phosphate pathway is the only source of nicotinamide adenine dinucleotide (NADPH), and defense mechanisms against oxidative damage are highly dependent on G6PD activity. The occurrence of acute haemolysis in patient with G6PD deficiency and diabetes has been reported and ascribed to various mechanisms. Her we report a case of patient with G6PD deficiency that his diabetes was revealed by haemolysis crisis.
Case report
A 58-year-old man, who had a G6PD deficiency in its hemizygous form, treated with folic acid, was admitted for acute haemolysis following consumption of beans. He complained of fatigue, polyuria, blurred vision of one month. He had lost a weight and his body mass index was 30 kg/m^2. Physical examination was unremarkable. Plasma glucose concentration was 18 mmol/l and ketonuria was 2+. G6PD activity was decreased to 7% of the lowest normal value. The patient was treated with fluids and potassium replacement, and intravenous insulin. He rapidly recovered and good glycaemic control was obtained with subcutaneous insulin injection. After a 4-year follow-up, diabetes was controlled (mea capillary blood glucose 6 mmol/l, HbA1C 5.9%) with diet and insulin, and no relapses of haemolysis has occurred (blood haemoglobin 14.6 g/dL, total bilirubin 8 µmol/l). Also, He was treated for arterial hypertension with converting enzyme inhibitor, hydrochlorothiazide and bisoprolol, and for ischemic stroke with salicylic acid and statin.
Conclusion
Experimentally, hyperglycemia decreases the expression of the G6PD gene and the activity of his enzyme. Conversely, G6PD deficiency promotes oxidative stress and disrupts the secretion of insulin by beta cells. In subjects at risk of G6PD deficiency, hemolysis should be sought following diabetes decompensation. These two pathologies can worsen reciprocally. An etiological link between them is plausible.

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AEP443

Results of survey of patients trained in the outpatient diabetes school

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Background
Constant feedback is required for optimal performance, allowing for flexible planning of outpatient diabetes schools.
Aim
To study patient satisfaction with the results of education in the outpatient school for type 1 diabetes (s.d.).
Materials and methods
96 patients with type 1 diabetes (T1D) were included. The survey contained 5 questions: Have patients previously been trained at the s.d.? Which sources do they use to receive information? Does the patient suppose that he has enough knowledge about diabetes? Does the patient fully implement the doctor's recommendations? What is a convenient time for attending classes? Does the patient is involved in social networks?
Results
74.5% of the patients surveyed had previously received training at the s.d. 32.26% had been trained more than 3 years ago. 54,84% had undergone training in hospital. 3,22% have been trained in s.d. 67.74% regularly receive information from their attending endocrinologist. 29.03% – from books on the T1D. 58.06% – from the Internet. 22.58% – from other patients with the T1D. 61.3% consider they have enough knowledge about T1D. There's not enough knowledge: 12.9% do not know why they have hypoglycemia; 16.3% are not sure about the correctness of BU calculation and selection of insulin doses; 20,0% are not sure that they can help themselves with hypoglycemia; 12.9% are in need of an individual diet and food selection; 3.22% do not know enough about foot care. 70.91% of patients believe that they are implementing all the doctor's recommendations; not following the recommendations: 9.68% do not follow the nutrition recommendation; 16.1% do not follow the recommendations for physical activity; 12.9% do not keep a self-control diary; 3.2% break the date of appointment for a second medical examination; 3.2% do not perform frequent self-control due to lack of test strips. 3.22% of patients are ready to attend classes daily. 6.45% of patients are ready to attend classes every day. 51.61% of patients are more comfortable attending classes once a week (on Saturdays).
Conclusion
Patients with T1D type have insufficient knowledge on the prevention of acute complications, calculating CE and insulin doses, ready to visit classes on diabetes and most of them suppose they have enough knowledge about diabetes.

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AEP444

Factors associated with being underweight among diabetic outpatient in Cotonou

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Introduction
Under-nutrition is a greater risk factor for low productivity andpoor health as diabetes[1]. In Benin 11.9% of males and 9.5% of females were underweight[2] and 5.3% of the population have diabetes[3]. There is no data available on underweight among diabetic in Benin.
The aim of this study is to determine the prevalence of underweight among diabetic and the associated factors.
Method
It was a cross sectional study including 408 diabetics followed up at Cotonou. They have benefited from food survey including a 24 hour dietary recall, the rating of a consumption score then anthropometric measurements. The energy intake was evaluated by the software 'Alimenthèque' and compared to the energy requirements determined by Harris and Benedict's formula. The under weight was defined by BMI < 18 kg/m^2.
Result
The average age of patients was 54.95 ± 0.61 years with a female male sex ratio of 2.11. The prevalence of underweight was 4.67%. The average age of diabetics with weight deficit was significantly higher: 57.26 vs 48.23 years. Factors associated with underweight in multivariate analysis are single diabetics, those with low energy intake, and those with moderate and low food diversification.
Discussion and conclusion
This study suggests a lower prevalence of underweight among diabetic patients compared to the general population. This is partly explained by the urban site of this study, because the current nutritional transition in the sub-Saharan region is mostly urban[4]. These results also highlight the importance of nutritional assessment and survey for diabetic patients in particular those belonging to a vulnerable group: elderly patients, single patients.
Key words: Underweight, diabetes, Cotonou.
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AEP445

Prevalence of dyslipidemia in elderly diabetics

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Introduction
Diabetes in the elderly is often accompanied by other comorbidities, particularly dyslipidemia, which considerably increases the cardiovascular risk in these patients.
The aim of our work was to determine the lipid profile in elderly diabetic subjects.
Methods
This was a descriptive and analytical study carried out on 100 elderly type 2 diabetics hospitalized in our department for unbalanced diabetes. Each patient underwent a complete clinical examination, a biological assessment including the lipid assessment with a complete assessment of the impact of diabetes.
Results
The average age of our population was 69.36 years with a predominance of the age group ranging from 65 to 70 years (56%). There is a clear female predominance (74%). The average BMI was 26.7 kg/m^2. Only 14% of this population had a low socio-economic level. The majority had retained their autonomy (90%). The average duration of progression of diabetes was 15 years with an average HBA1c of 10.2%, of which 54% were on insulin therapy. The mean cholesterolemia was 4.89±1.02 mmol/l, the mean triglyceridemia was 2.27±1.22 mmol/l and the mean LDLemia was 2.24±0.4 mmol/l. Our patients had isolated hypercholesterolemia in 11.2% of cases, hyper LD Lemia in 6.2% of cases and hypoHDLemia in 42.8% of cases. Isolated hypertriglyceridemia was noted in 14.8% of cases. Only 12% of our population had a correct lipid balance under treatment. The analytical study had not shown any positive association between the existence of dyslipidemia and the following factors: the level of HbA1c and the duration of diabetes.
Conclusion
Dyslipidemia is common in elderly diabetics, especially hypo-HDLemia and hypertriglyceridemia. Screening should be systematic and adequate management will prevent cardiovascular accidents.

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AEP446

Real-time continuous glucose monitoring impact on the metabolic control over the summer in children with type 1 diabetes

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Background
Type 1 diabetes is a chronic disease requiring constant management and a disciplined lifestyle, especially in children. Real-time continuous glucose monitoring system (RT-CGMS) can be a useful tool in maintaining good glycemic control. In our medical centre, beginning with January 2019, a National Program for free distribution of RT-CGMS has been set in motion. The results from one of our previous studies indicated a significant increase in glycosylated haemoglobin (HbA1c) levels after 6 months from RT-CGMS initiation in children already on RT-CGMS at baseline, presumptuously due to a poor metabolic control during the summer months. The present study analyses this hypothesis.
Methods and materials
The analysis included 73 patients, aged under 18 upon entering the national program, who were divided into two groups, depending on the existence of a RT-CGMS at baseline: with previous RT-CGMS at baseline (RT-CGMS+) and without a RT-CGMS at baseline (RT-CGMS-). The baseline medical visit for these patients was done in June and July 2019 when they received free glucose monitoring sensors. The 3 months visit was considered at 90±30 days from baseline. This is a unicentric, prospective cohort study.
Results
We evaluated 73 patients, 36 women (49.3%), mean age 11.2±3.8 years (range: 2.3–17.8 years), mean diabetes duration 4.7±3.1 years. The RT-CGMS+group has 26 subjects, mean age 11.1±4.1 years, mean diabetes duration 5.4±3.1 years, with a mean HbA1c 7.0±0.5% (53 mmol/mol) at baseline. The RT-CGMS- group has 47 subjects, mean age 11.3±3.6 years (P=0.90 vs RT-CGMS+), diabetes duration 4.3±3.1 years, and HbA1c 7.6±1.1% (60 mmol/mol, P=0,016 vs RT-CGMS+) at baseline. There was a significant increase in HbA1c after 90.2±8.1 days in the RT-CGMS+ group reaching 7.5±0.6% (58 mmol/mol, P<0.01 vs baseline). The HbA1c variation did not change significantly in the RT-CGMS- group, with a value at 3 months of 7.8±1.1% (62 mmol/mol, P=0.075 vs baseline).
Conclusions
The results of the three months follow-up over the summer for the two patient groups indicated that RT-CGMS initiation in patients previously not exposed to RT-CGMS cancels the increase of HbA1c levels registered in patients previously exposed to RT-CGMS, who continue to use it for the same study period. This finding is consistent with the poor glycemic control observed during the summer in most patients, and especially in teenagers.

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AEP447

The impact of real-time continuous glucose monitoring on metabolic control in children with type 1 diabetes

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Background
Real-Time Continuous Glucose Monitoring Systems (RT-CGMS) represent a minimally invasive method for frequent glucose monitoring, allowing a better glycemic control for patients with type 1 diabetes. With the occasion of implementing the National Program for free access to RT-CGMS, we assessed the 6 months impact of RT-CGMS on the metabolic control, evaluated by glycated haemoglobin (HbA1c).
Methods
In this unicentric, prospective cohort study, we assigned patients with type 1 diabetes, aged less than 18 years, receiving the free RT-CGMS from a pediatric diabetes centre and returning for the 6 months resupply visit by January 9th, 2020. The allowed 6 months visit window was ±30 days. Patients were divided into two groups according to whether they already had a RT-CGMS at baseline or not: RT-CGMS+ (with RT-CGMS already used at baseline) and RT-CGMS- (without RT-CGMS at baseline).
Results
The study was completed by 63 patients, 28 women (44.4%), mean age 10.1±3.8 (range: 3.1–17.9) years, mean diabetes duration at baseline 5.1±3.4 years, who were evaluated at baseline and at 180.8±11.5 days. The RT-CGMS+ group had 31 patients, mean age 9.9±3.7 years, mean diabetes duration 5.2±3.0 years, mean HbA1c at baseline 7.3±0.7% (56 mmol/mol). The RT-CGMS- group had 32 patients, mean age 10.3±3.9 years (P=0.67 vs RT-CGMS+), mean diabetes duration 4.9±3.8 years (P=0.73 vs RT-CGMS+), and baseline HbA1c 7.9±1.1% (63 mmol/mol, P<0.01 vs RT-CGMS+). The HbA1c significantly rose at 6 months in RTCGMS+ group to 7.5±0.7% (58 mmol/mol, P<0.01 vs baseline). However, in the RT-CGMS- group, the HbA1c didn't have a significant change at 6 months, reaching 8.0±1.0% (64 mmol/mol, P=0.71 vs baseline).
Conclusions
The introduction of a RT-CGMS to patients without previous access to this technology was associated with a complete resolution of the natural tendency towards an increase in HbA1c at 6 months, which was seen in patients already using a RT-CGMS and continued to use it for another 6 months. A possible explanation for the HbA1c increase registered in children already on RT-CGMS at baseline might be the effect of summer months when diabetes management was possible less stringent. Further work is needed to verify this hypothesis.

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Phospholipid metabolism in patients with type I and 2 diabetes mellitus

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The onset of diabetes mellitus caused by insulin deficiency and insulin resistance is simultaneous with the onset of disorders in lipid and carbohydrate metabolism. Phospholipids are subjected to major alterations in the lipid structures. The data on composition of phospholipids in diabetes mellitus are discordant. The work was initiated to study concentrations of phospholipids in blood of patients with type 1 and type 2 diabetes mellitus. 24 patients with type 1 DM (T1DM) and 34 patients with type 2 DM (T2DM) were recruited for the study. Blood glucose, lipid profiles and blood serum phospholipids were measured. The chloroform-methanol mixture was used to extract the phospholipids. Thin-layer chromatography was used to fractionate them. In patients with T2DM the total phospholipid fractions were found to decrease as compared to the controls (103.63±4.744 μg of phosphorus/mg of protein vs 207.6±4.4 μg of phosphorus/mg of protein). In T1DM patients the total phospholipid fractions were reduced as compared to the controls. As to individual phospholipid fractions in T1DM and T2DM, the alterations were found oppositely directed. Thus, acidic phospholipids, such as phosphatidylinositol (PI) and sphingomyelin (SPH) increased, while the neutral ones, to name phosphatidylethanolamine (PE) and phosphatidylcholine (PC) decreased as compared to the controls. Intensity of acyl residuals of all phospholipid fractions is subject to alterations in insulin deficiency. Transacylation as a chain-termination in fatty acid synthesis in phospholipids is impaired due to inhibition of the acylase reaction with activation of phospholipases to result in suppression of acyl group synthesis. The reduction in synthesis of choline-containing phospholipids can be explained by the disorders in methylation of phosphatidylethanolamine which is a precursor in the process. Failure of the metabolic pathways to reuse exogenous choline due to the deficiency of ATP, A coenzyme, pyridoxal phosphate and other co-factors of lipid metabolism in insulin deficiency could be another cause for the disorder of phospholipid synthesis in diabetes. The increase in lysophosphatidylcholine in diabetes can be associated with the peroxidation of phosphatidylcholine and the disorders in diacyl phospholipid forms. Disorders in major and minor components of phospholipids take place in type 1 DM and type 2 DM. As the result, concentrations of total phospholipids change to result in the lipid metabolism dysregulation.

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High prevalence of psychiatric disorders and its association with worse glycemic control in patients with type 1 diabetes

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Introduction
Chronic diseases such as type 1 diabetes can be associated with psychiatric disorders. Previous data suggest a high prevalence of depression, anxiety, disordered eating and diabetes distress among patients with diabetes. Mental health problems could interfere with treatment adherence, glucose control and chronic complications.
Objective
We aim to evaluate the prevalence of psychiatric disorders, drug abuse, and treatment adherence in patients with type 1 diabetes. We also aim to study the association of mental health problems with glycemic control and chronic complications.
Methods
A cross-sectional study was designed to apply face-to-face standardized questionnaires and to evaluate patients' clinical data from medical records. We included patients with type 1 diabetes over the age of 10 who are assisted at two public hospitals linked to federal universities in Southern Brazil. Patients signed a consent form and the study was approved by Ethics Committee. We used Patient Health Questionnaire-2 (PHQ) and PHQ-9 to evaluate depression, Self Care Inventory-Revised to evaluate treatment adherence, and Eating Attitudes Test to study eating disorders. We also apply a questionnaire to investigate licit and illicit drugs use and anxiety symptoms.
Results
We included 166 patients with a median of 33 years (22–45 years), 53.6% were women, with a median of 14 years (6–25 years) since diabetes diagnosis, and a median of A1c of 8.5% (7.8–9.4%). 91 patients (54.8%) was diagnosed with one mental health disorders (20.5% of patients have depression and 40.4% have anxiety), and 79 (47.6%) patients had positive screening for eating disorder. About drug use, 16 (9.6%) patients are active smokers, 30 (18.1%) patients drink alcohol regularly, and 2 (1.2%) patients use illicit drugs. The comparison between patients with and without psychiatric illness showed a worse glycemic control in the group with mental disorder (A1c 9.0% vs 8.5% in controls); there was no other clinical or laboratorial difference between groups. Patients with suicidal ideation or attempt are almost entirely depressed (34 patients [94.4%]). 91 patients (54.8%) were considered to have good adeherence to treatment; this group of patients has a better A1c than non-adherent patients (8.4% vs 8.8%; $P=0.023$).
Discussion
The prevalences of psychiatric illness, drug use and eating disorders are high among patients with type 1 diabetes and it is associated with a worse glycemic control. Clinical doctors should be aware of this scenario and, therefore, do screening for mental disorders in this population.

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Congenital anomaly of the kidney and urinary tract and mody 5 due to 17Q12 deletion syndrome; a case report

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Hepatocyte nuclear factor 1B (*HNF1B*) defects (mutations or deletion) are associated with amultisystem disorder, including urinary tract abnormalities and diabetes (MODY 5, maturity-onset diabetes of the young type 5). We present the case of a patient with congenital anomalies of the kidney and urinary tract in the context of 17q12 deletion syndrome who several years later, presented with MODY 5. A 20-year-old male presented at the outpatient Endocrine Clinic with new-onset diabetes mellitus. Laboratory findings revealed a HbA1c of 7.9%, with no evidence of ketoacidosis, detectable C- peptide levels (2.3 ng/ml) and negative antibodies to glutamic acid decarboxylase (GAD), tyrosine phospahtase (IA2) and insulin (IAA). He had a history of right ureterovesical junction obstruction repaired at the age of 2 and persistent hypomagnesemia, hypermagnesuria and hypocalciuria were found at the age of 15. A deletion of 1.4 Mb at chromosomal band 17q12 was then detected by array-comparative genomic hybridization, encompassing two OMIM genes, the Acetyl-CoaCarboxylase-Alpha (ACACA, OMIM#200350) and Hepatocyte Nuclear Factor-1-B (HNF-1B, OMIM#1890907). Elevated liver enzymes had been noted since the age of 17, and hypoplasia of the pancreas had been detected on an MRI scan. In addition, the patient exhibited learning difficulties, and mild mental retardation had been documented at the age of 16 (Wechsler Intelligence Scale III-R Full scale IQ score: 58). Based on the phenotypic features and results of the genetic analysis, a diagnosis of 17q12 deletion syndrome was made. The 17q12 deletion syndrome is caused by deletion of a 1.4 Mb region of 17q12 which encompasses genes like *HNF-1B, ACACA* and *LHX1*. Clinical features include diabetes mellitus of the MODY 5 type, functional and structural kidney and urinary tract disorders, cholestatic hepatopathy, structural pancreas malformations, intellectual/learning disabilities, neuropsychiatric disorders and facial dysmorphia. Recent evidence suggests that MODY 5 is a common feature in patients with 17q12 deletion syndrome whilston the other hand, whole gene *HNF1B* deletions are observed in up to 50% of MODY 5 cases. Notably, as recently reported by Laffargue *et al.*, complete deletion of the *HNF1B* gene and 17q12 microdeletion syndrome may be considered as the same genetic disorder (5). Clinical features suggestive of the 17q12 deletion syndrome should prompt clinicians to request chromosomal microarray analysis in patients with suspected MODY 5.

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Sleep quality of diabetic patients with metabolic syndrome, is therea difference?

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Objective
Poor sleep quality is a prevalent health problem among patients with diabetes. Metabolic syndrome (MetS) is common in type 2 diabetic patients, and associated with morbidity and mortality. We aimed to investigate sleep quality among type 2 diabetes patients according to their metabolic syndrome status.
Participants
This was an analysis of data collected from 189 adult type 2 diabetic patients.
Methods
The patients were divided into two groups (metabolic and non-metabolic) based on the presence of MetS. Anthropometric measurements, blood pressure and serum glucose, lipid levels were collected. The Pittsburgh Sleep Quality Index (PSQI) was calculated for all patients .
Results
There was no significant difference in subjective sleep quality scores between the two groups ($P>0.05$). However, there was a significant difference in sleep latency scores between the two groups; the scores of patients with MetS were lower than those of patients without MetS ($P=0.010$, $P<0.05$). Sleep quality was low in 57.1% ($n=108$) of the patients with diabetes.
Conclusions
Poor sleep is common among diabetic patients, but in this study metabolic syndrome existence was not associated with sleep quality in type 2 diabetic patients.

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Retinol-binding protein in the diagnosis nafld and type 2 diabetes

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Retinol binding protein (RBP) is an adipokine, related to insulin resistance (IR). Excess free fat acid reduces the binding of insulin by hepatocyte receptors and leads to hyperinsulinemia. RBP transport protein synthesized in hepatocytes and adipocytes. The level of RBP increases in patients with obesity, diabetes and non-alcoholic fatty liver disease (NAFLD). It is positively correlated with the degree of severity of the inflammatory process and fibrosis. The RBP regulates the activity of insulin in tissues, skeletal muscles, and the liver.
Purpose of research
Determine RBP in patients with NAFLD and type 2 diabetes. Compare the results of RBP with markers of lipoprotein-associated inflammation phospholipase (FLA2) and nitrogen oxide (NO), which inhibits the proliferation of collagen and regulates hepatic blood flow.
Material and methods
208 patients with NAFLD and type 2 diabetes were examined. The average age is 57.3±5.2. There were 76 patients with type 2 diabetes and 132 with impaired glucose tolerance (NTG). BMI more than 30 kg/m^2 (34.85±1.79). Clinical, biochemical, and instrumental research methods were performed. RBP was determined in 89 patients with type 2 diabetes using the immunoassay method in blood serum. The control group consisted of 15 practically healthy person. FLA was determined by immunoenzyme method. NO metabolites were determined by Express method.
Research result
The RBP content in the control group was 26.15±1.31 mg/l. The RBP content in patients with type 2 diabetes without NAFLD (group 1) was reduced by 12.8% and amounted to 20.34±3.8 mg/l. The RBP content in 49 patients with NAFLD and2 diabetes (group 2) was significantly increased by 48.9% and amounted to 38.96±11.47 mg/l. The FLA2 content was increased by 4.78 times in relation to the control in group 2. The content level stable nitric oxide metabolites was increased in parallel with liver activity enzymes. There is a direct positive correlation between FLA2 and NO. The correlation coefficient was $r=0.625$ $P=0.001$.
Conclusion
The level of RBP was significantly increased in patients with type 2 diabetes and NAFLD compared with control and group 1. Increase in the content of inflammatory markers accompanied by an inflammatory process in the liver with increased activity liver enzymes and the severity of morphological changes.

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Prevalence of disordered eating behaviour in type 2 diabetic patients receiving insulin

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Objective
Diabetes mellitus represent a demanding set of biopsychosocial challenges(-depression, anxiety disorders, eating disorders) for patients and their families regardless of the age of disease onset. Disordered eating behaviors and eating disorders(ED) represent a spectrum of symptoms that may include restricted caloric intake, distorted body image, binge eating and/or purging behaviors such as excessive exercise, vomiting, and the use of laxatives to lose weight. The prevalence of eating disturbances varies and depends on studied population (age, BMI) and used methods of diagnosis. The aim of the study was to assess the prevalence of disordered eating behavior in type 2 diabetes mellitus(DM) patients received insulin using EAT-26 questionnaire.
Method
263 patients with type 2 DM receiving insulin were examined. The mean age was 62 (57–67) years, mean weight 91 (78–105) kg, duration of diabetes mellitus 12 (8–17) years. The group of women consisted of 186 patients (the mean age 62 (57–58) years, the mean duration of DM 12 (7–18) years), the group of men include 77 patients (mean age 60 (56–66) years, duration of DM 12 (8–16) years). There were no statistic differences in age ($U=11088$, 5 $P=0.077$), BMI ($U=11659$, 0 $P=0$, 276), duration of DM ($U=8461$, 5 $P=0.800$) in the subgroups. Our study assess the prevalence of ED by using EAT-26 questionnaire as a screening instrument. The cut off 20 was used as a criteria for diagnosis.
Results
The prevalence of disordered eating behavior according to the results of cut off EAT-26 questionnaire was 35.3% (93 of 263 patients had the score 20 and higher). The mean score of EAT-26 was 15 (9–21). Statistical differences were revealed in the EAT –26 score depending on gender ($U=5453.0$ $P=0.002$). The mean EAT score in subgroup of men was lower 12 (7–20) than in the subgroup of women 16 (10–22). The prevalence of disordered eating in the subgroup of men was 25, 9% (20 of 77 patients). In the subgroup of women 39, 2% (73 of 186 patients).
Conclusion
The prevalence of disordered eating behavior in type 2 DM receiving insulin patients tested by EAT-26 questionnaire was 35.3%.

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Constructing a model for the differential diagnosis MODY diabetes and type 2 diabetes

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Most young patients with hyperglycemia are diagnosed with type 1 diabetes mellitus and type 2 diabetes mellitus (T2DM) but up to 10% of all cases of the disease occur in MODY diabetes. Diagnosis of the correct type of diabetes mellitus (DM) leads to the appointment of pathogenetic effective therapy, adequate management of pregnancy and the prevention of specific complications. The aim of the study was to create a model for the differential diagnosis of T2DM and MODY.

Materials and methods
We examined 108 people in Novosibirsk city who had debut of DM up to 35 years: 92 patients has been confirmed by molecular – genetic testing MODY, 91 – type 2. All patients had a clinical examination, blood sampling for biochemical and hormone (TSH, C-peptide) analyzes. A model was constructed to study the most significant factors during the diagnosis of type of diabetes using binary logistic regression.
Results
Both groups of patients were comparable in gender, age, and duration of diabetes. Median of age of the patients at moment of examination was with T2DM – 29.5 [17.7;37.0] years, with MODY – 24.0 [0.0;35.0] years ($P=0.280$). After creating various regression models the most significant factors associated with diabetes were identified: 'the presence of relatives with diagnosed diabetes for them under 35 years of age', 'the presence of relatives with impaired carbohydrate metabolism and obesity', 'overweight and obesity'. A final regression model is constructed to determine the significance of these factors. Among the analyzed factors associated with the type of diabetes all three were statistically significant ($P<0.001$).
Thus when studying the influence of a hereditary history, clinical and laboratory factors in MODY and T2DM during the construction of binary regression models it was determined that the presence of relatives with verification of hyperglycemia up to 35 years was associated with MODY diabetes and the presence of excess weight and obesity in patients with T2DM as well as relatives with diabetes and obesity. These results should be taken into account when conducting differential diagnosis of the type of diabetes mellitus in individuals with diagnosed hyperglycemia up to 35 years.

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Acidosis is not a sine qua non for DKA

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Although Diabetic ketoalkalosis (DKAlk) has beendescribed as a mixed acid-base disorder over half a century ago, there is unawareness among physicians. Here, we present two cases to emphasize DKAlk which is more common than it's thought.
Case-1
A thirty-year-old female patient with type-1 diabetes and ten weeks of pregnancy presented with several weeks of vomiting. She also reported that she had hyperthyroidism for 2 weeks and that she used propylthiouracil 50 mg/day in addition to insulin. Physical examination revealed volume depletion findings such as dehydration andtachycardia. Laboratory findings are shown in the table. These findings suggested metabolic acidosis masked by alkalosis. Fluid replacement and insulin infusion therapy was applied rapidly. Propylthiouracil was increased to 150 mg/day, in addition to iodine restriction. After 3 days, ketonuria disappeared and pH and delta gap were found as 7,44 and 13,5, respectively. In this case, the acid-base disorders were DKA, metabolic alkalosis due to hyperemesis gravidarum and respiratory alkalosis due to pregnancy and gestational thyrotoxicosis.
Case-2
A thirty-two-year-old female patient with type-1 diabetes and sixteen weeks of pregnancy was admitted to emergency department with vomiting, dysuria and sore throat. She had hypotension andtachycardia as results of severe dehydration. Laboratory findings are shown in the table. She also had pyuria and high levels of CRP (42.99 mg/l) and ESR (85 mm/h). These results were compatible with combined alkalosis and acidosis. After 24-hour fluid replacement, insulin infusion and ceftriaxone therapy, hypovolemia improved, ketonuria disappeared, glucose levels returned to normal range. While clinical situation improved within days, all other laboratory results ameliorated. Thyroid disorder was interpreted as subacute thyroiditis and followed without treatment; fT4 and fT3 levels decreased spontaneously at the end of the second week (fT4:11.29 pmol/l, fT3:3.88 pmol/l). In this case DKA, metabolic alkalosis due to vomiting caused by acute pyelonephritis and respiratory alkalosis due to pregnancy and thyroiditis were observed. As conclusion, acidosis is not a sine qua non for DKA. Awareness should be raised about DKAlk. It should always be kept in mind that mixed acid-base disorders can mask DKA and DKAlk may be in the foreground of the picture.

	pH	HCO3 (mEq/l)	PCO2 (mmHg)	keton-uria	Glucose (mg/dl)	WBC/neu	Crea (mg/dl)	Na/K/Cl (mmol/l)	Anion gap	Delta gap	TSH (mIU/l)	fT4/fT3 (pmol/l)
Case-1	7.55	27.3	29.7	+++	413	14 600/mcl /84,4%	1.53	134/4.84/88.1	16.2	20.9	0.005	81.9/ 15.08
Case-2	7.50	28.3	35	+++	682	15 900/mcl /85,8%	2.1	132/3.87/72.4	31.3	34.6	0.026	26.94/ 7.72

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Effect of dietary intake of branched chain amino acids on type 2 diabetic patients

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Background
BCAAs up regulate glucose transporters and activate insulin secretion has been widely demonstrated. However, several researchers have suggested that excessive intake of amino acids could lead to inhibition ofinsulin signalling. BCAAs may induce insulin resistance throughm TOR activation insulin resistance may be linked with high intake of BCAAs, Controversiesremain on whether an increase in plasma BCAA levels is a cause or consequence of insulin resistance.
Aim
The aim of the study is to measure the effect of consumption ofBCCAs on lipid profile and glucose level in type 2 obesediabetic patients.
Subject and methods
Participants enrolled in the study 280 patients (139 male,141 female) with type 2 diabetes formore than 5 years. Attending Endocrinology out patient clinic. Written consent was obtained from all participants. Anthropometric measurement (height, weight, waist circumference, body mass index. Dietaryassessmentparticipants had to complete food frequency questionnaire (24 hour recall) for 5 days and analysis for branched chain amino acid intake wasperformed using food composition table, life style, socio-demographic level, laboratory investigations including, fasting glucose, HbA1c, cholesterol, triglyceride, LDL, HDL.
Results
Mean Age 38.24±4.28, male 49.6%, female 50.4%, diabetes duration 8.86±2.26 years, BMI; 29.89±3.02, protein intake 77.75±14.76 g, Leucine 4.75±1.01g, valine 4.04±0.89 g, Isoleucine 4.09±0.92 g, fasting glucose 206.60±51.01 mg. A1C 9.33±1.18, cholesterol 238.79±40.37 mg/dl, triglycerides 103.47±14.01 mg/dl. LDL178.20±43.32 mg/dl/HDL 44.03±9.55 mg/dl. All of our patients took higher load for age and ideal weight of (leucine, valine, and isoleucine is likely to be 0.04, 0.017–0.02, and 0.019 g/kg respective) mainly from plant source protein. Regarding correlation with A1C (Valine $P=0.01$, $r=0.02$/isoliosine $P=0.08$ $r=0.156$). Regarding correlation with LDL (liosine $P=0.07$ $r=0.156$).
Conclusion
High BCCAs intake mainly from plant source is associated with dyslipidaemia and poor glycaemic control proper dietary counselling is important in diabetic.

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Real-life clinical experience with GLP1 analogs and SGLT2 inhibitors in the treatment of diabetes type 2 and obesity

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Objectives
SGLT2 inhibitors and GLP1 analogs are the treatment of choice after metformin in patients with type 2 diabetes (DM2) and overweight-obesity (OB).

The aim of this study is to analyze the effectiveness and safety of these treatments alone or in combination.
Methodology
This is a retrospective observational study in the usual clinical practice. We analyzed the effects of SGLT2 inhibitors and GLP1 analogs treatments in patients with DM2 and OB who have poor metabolic control after metformin. We measured: HbA1c, weight, insulin dose, systolic blood pressure and LDL cholesterol levels at 0, 3, 9 and 15 months. Likewise the proportion of adverse effects were registered.
Results
A total of 90 patients, 48 men and 42 women, with a average age of 62.7±9.7 years were analyzed. At the beginning they had an average BMI of 35.6±7.0 kg/m^2 andHbA1c of 7.9±1.1%. The average evolution time of DM2 was 12.2±9.4 years and 68.9% patients were insulin dependent with an average initial insulin dose of 37.3±2.6 IU. 23.3% of patients were treated with GLP1 analogs (liraglutide, lisixenatide, weekly exenatide, or dulaglutide), 55.6% were treated with SGLT2 inhibitors (dapaglifozin, canaglifozine, or empaglifozine) and 21.1% with a sequential combination of both. Regarding metabolic control, we observed a significant reduction in HbA1c at 3 months: –0.61±1.20% (P<0.001), at 9 months: –0.70±1.12% (P<0.001) and at 15 months: –0.73±1.31% (P=0.004). Regarding weight, we also found a significant improvement at 3 months: –2.13±2.63 kg (P<0.001), at 9 months: –3.63±3, 07 kg (P<0.001) and at 15 months: –3.83±4.14 kg (P<0.001). Insulinized patients required significantly lower doses of insulin at 3 months: –3.62±7.95 IU (P=0.001) and at 9 months: –6.45±12.16 UI (P=0.002), without reaching statistical significance at 15 months: –6.50±17.81 UI (P=0.12). We didn´t observe significant changes in systolic blood pressure and LDL levels. Finally, we registered adverse effects in iSGLT-2 patients: genital mycosis in 7.8% and urinary tract infections in 4.4%; andina GLP-1 patients: vomiting in 1.1%.
Conclusions
The results of this study corroborate the benefits obtainedin clinical trials with the GLP1 analogs and SGLT2 inhibitors in metabolic and weight control, with a low rate of adverse effects.

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Glucose scan behaviour in people with type 1 diabetes using flash glucose monitoring in a real-world setting

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Introduction
Flash glucose monitoring (FGM) enables people with diabetes to regularly track their glucose levels without performing capillary finger-stick measurements (SMBG). Clinical studies have shown improvement in glycemic control, reduction of hypoglycemia, improvement in comfort and quality of life in people with type 1 diabetes (T1D) using this technology. In contrast to continuous glucose monitoring, FGM requires the performance of a scan to obtain the current glucose level. The analysis aimed to investigate whether patients' scanning behaviour alters closer to an outpatient clinic visit.
Methods
We analysed registry data collected by at tertiary diabetes centre in Austria. People with T1D routinely using FGM to manage their diabetes were included in the analysis. FGM data of the last 90 days before a routine outpatient clinic visit were analysed. We assessed the effect of scan frequency on parameters of glycemic control such as eA1c (estimated A1c) and time in range (TIR) two weeks and three months prior to consultation. We tested for normal distribution using Shapiro-Wilk test and compared scan frequency, changes in eA1c and TIR using paired two-sample t-test.
Results
Data from 89 individuals (49% female, age 42.3±13.9 years, BMI 25.1±4.0 kg/m^2, diabetes duration 20.1±12.5 years, CSII vs MDI 18 vs 71) were analysed. Data are two weeks vs three months before a regular outpatient clinic visit, respectively. The mean scan frequency was 13.2±8.3 scans/day vs 10.5±4.4 scans/day (P<0.01). EA1c 58.9±11.8 mmol/mol vs 59.2±10.7 mmol/mol (P=0.664) and TIR (70–180 mg/dl) 53.9±16.3% vs 53.11±14.8% (P=0.346) were not significantly different between the two time periods.
Discussion
We observed a significant increase in daily scan frequency two weeks prior to a scheduled outpatient clinic visit as compared to the three months before the visit This is analogous to earlier findings in SMBG, showing an increase in performance and documentation of glucose values before an outpatient clinic visit. Despite this increase in glucose checks, there was no significant improvement in glycemic control assessed by FGM such as eA1c and TIR. The recommended treatment goal of >70% TIR 70–180 mg/dl was not achieved in our population. Thus, we can assume that only an increase in scan frequency might not necessarily result in relevant improvement in glycemic control. Therefore, effort must be made to motivate and educate FGM users better to make use of the full potential of FGM.

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AEP459

Mediterranean diet as a novel adjuvant treatment for type 1 diabetes

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Introduction
The importance of good glycaemic control in Type 1 diabetes (T1D), including its association with reduced cardiovascular disease, is well established. Current education programs focus on carbohydrate counting and its matching to the insulin dose. We set out to investigate the association between Mediterranean diet (MD) and the glycaemic control in patients with T1D.
Study design
This was a cross-sectional study that was a collaboration between Cyprus and the UK, which recruited patients with T1D from Limassol, Cyprus. The sample was randomly selected from the database of the Cyprus Diabetes Patients' Association.
Statistics
The MD was examined for its association with glycaemic control through a predefined multivariate linear (OLS) regression model. The MD was measured through a priori Mediterranean diet score, namely MedDietScore and the glycaemic control through HbA1c and fasting glucose. The covariates were gender, age, BMI, C-peptide, household income, injection method, smoking status and insulin adjustment to carbohydrate intake. Statistics were analysed using STATA 16.0.
Ethics
Ethics approval was received from the Cyprus National Bioethics Committee (EEBK/EII2016/09) and from the University of Stirling, UK (NICR 16/17 – Paper No.44).
Results
The study recruited 103 participants (median age 33 yrs (IQR 26,43); 51 males). Themean MD score was 31.7 (s.d.±5.7) points with a median HbA1c at 60 mmol/mol (51,74) and fasting glucose at 168 mg/dl (102,247). The adherence to the MD was significantly associated with HbA1c [b=–0.015, (–0.026, –0.0045), P=0.006] but not with fasting glucose. The OLS model predicted a reduction in HbA1c (mmol/mol) by 1.5% for every additional point in the MedDietScore scoring system. A post-hoc analysis indicated that the fasting glucose did not mediate the effect of the MD on the HbA1c: the indirect effect (simple mediation analysis) was not statistically significant (b=–0.0027, P=0.180) and when fasting glucose was added to the OLS model, the prediction power of MD on HbA1c remained largely unchanged (b=–0.014, P=0.005).
Conclusion
Patients with T1D in Cyprus appear to have a modest adherence to the MD, with a concerning low uptake in the younger subpopulation. Adherence to the MD was significantly associated with HbA1c and the predicted change was clinically significant. This improvement in HbA1c is more likely mediated via the non-fasting glucose excursions. The adoption of the MD should be encouraged in the structured education programs for T1D.

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AEP460

Impact of interval walking training on albuminuria and leptin/adiponectin ratio in patients with type 2 diabetes mellitus

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Background
Physical activity is the first-line treatment in type 2 diabetes. Interval walking training has demonstrated good tolerability and more pronounced positive effects on physical fitness and metabolism in type 2 diabetes, compared to continuous walking. However, the effects of interval walking on vascular health markers, such as albuminuria, has not been extensively studied. Type 2 diabetes is associated with derangements in leptin/adiponectin axis, which might predispose affected individuals to vascular inflammation. The aim of this randomized controlled study was to investigate the effects of interval walking training delivered through smart mobile devices upon albuminuria and leptin/adiponectin ratio in patients with type 2 diabetes.
Methods
The study randomized patients with type 2 diabetes aged 35–75 into control ($n=26$) and interval training (IT, $n=14$) groups. Patients in IT group had to perform three 60-min interval walking sessions (3 min intervals of slow and fast walking with the intensity of 40% and 70% of the peak energy expenditure) *per* week delivered by smartphone application for four months. The adherence to training protocol was monitored remotely. Variables measured were albuminuria, leptin/adiponectin ratio, glycaemic control, lipid profile, anthropometric measures. Leptin and adiponectin concentration was measured in serum samples was measured by Luminex technology.
Results
In the IT group compared to control group, we observed a statistically significant decrease in albuminuria ($P=0.002$, interaction effect) and leptin/adiponectin ratio ($P=0.01$, interaction effect). As albuminuria and leptin/adiponectin ratio have been associated with progression of vascular complications of diabetes, our results indicate that interval walking training is effective for improvement of vascular health in diabetes.

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AEP461

The effect of empagliflozin treatment on biomarkers of fibrosis in patients with type 2 diabetes and a very high risk of cardiovascular events

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Objective
To evaluate the alterations of fibrosis biomarkers during empagliflozin treatment in patients with type 2 diabetes mellitus (T2DM) and a very high risk of cardiovascular events.
Materials and methods
Twenty-six patients with type 2 diabetes mellitus received 10 mg of empagliflozin within 24 weeks. Inclusion criteria: women and men aged 18 to 70 years with T2DM, glycated hemoglobin (HbA1c) 7.0–11.0%, stable hypoglycemic therapy at least 12 weeks before inclusion in the study, the presence of cardiovascular risk factors. Exclusion criteria: the presence of coronary heart disease, chronic heart failure or other clinically significant cardiovascular diseases, estimated glomerular filtration rate (GFR), according to CKD-EPI (GFR < 60 ml/min/1.73 m^2.). HbA1c, creatinine, galectin-3, tissue inhibitor of metalloproteinase-1 (TIMP-1), carboxyterminal propeptide of collagen type I (P1CP), matrix metalloproteinase-9 (MMP-9), ST-2, NT-proBNP, total cholesterol, LDL, HDL, triglycerides (TG) were evaluated.
Results
The age of the patients was 52 years (45–61), the HbA1c level at the time of the study inclusion was 8.6% (7.7–9.5), BMI 32.1 kg/m^2 (29.9–34.9). After 24 weeks of treatment, there was a significant decrease of HbA1c – 7.8% (7.2–8.1), $P=0.0001$ and BMI – 31.0 kg/m^2 (29.3–33.6), $P=0.002$. There were no significant differences between the concentrations of galectin-3 before treatment and after 24 weeks of treatment – 8.6 ng/ml (7.2–10.9) and 10.4 ng/ml (6.6–13.2), $P=0.571$. Significant differences were observed between the initial P1CP concentration and P1CP concentration after 24 weeks of treatment – 120.4 ng/ml (114.2–168.8) and 104.4 ng/ml (89.0–168.8) ($P=0.019$). However, after applying the Holm-Bonferroni, the differences were not significant. The concentrations of TIMP-1 after 6 months did not significantly differ compared with the initial values, 210 ng/ml (177–226) and 208 ng/ml (172–240), respectively, $P=0.861$. A significant negative correlation was obtained between the LDL concentration after 6 months of treatment and the ST-2 concentration after 6 months of treatment (LDL and ST ($r=-0.883$, $P=0.002$). A positive correlation was found between the initial concentration of galectin-3 and the initial concentration of SST ($r=0.501$, $P=0.02$).
Conclusions
Empagliflozin therapy for 24 weeks does not lead to a significant changes in fibrosis biomarkers, such as galectin-3, TIMP-1, P1CP, MMP-9, ST-2 in patients with type 2 diabetes and a very high risk of cardiovascular events.

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AEP462

Effects of semaglutide on glycemic control and body composition in patients with type 2 diabetes mellitus and obesity in a real life setting in spain

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Introduction
Semaglutide is a GLP1 receptor agonist (GLP1RA) recently approved in Spain for the treatment of Type 2 Diabetes (T2D) and the National Health Service finances it for patients with T2D and body mass index (BMI) > 30 with a poor metabolic control with metformin.
Objectives
Evaluate the effects of Semaglutide on glycemic control and body composition in patients with T2D (PwT2D) and obesity after 6 months of use in a real life setting.
Material and methods
This is a retrospective observational study. We included PwT2D and obesity without prior treatment with GLP1RA, who started semaglutide treatment (added to other antidiabetic drugs) between May 2019 and July 2019 in our clinic and maintained it for at least 6 months. Anthropometric measurements (including body composition when available – estimated with bioimpedance Inbody270), fasting glucose (FG) and glycated hemoglobin (HbA1c) were collected at baseline and at 6 months. Statistical analysis was performed with STATA 14. Paired T-student test for comparison between baseline and 6 months and logistic regression to evaluate Semaglutide dose (≤0.5 and 1.0 mg), age, sex, duration of T2DM, BMI and HbA1c at baseline as possible predictors of Semaglutide efficacy to achieve HbA1c < 7%.
Results
We included 75 patients (62% men), with a mean age of 62.3 ± 9.2 years and a mean duration of T2D of 11.3 ± 7.4 years. The maximum weekly dose of semaglutide used were: 0.25 mg (2.7%), 0.5 mg (85.3%), 1 mg (12%). After 6 months of treatment, there was significant improvement of glycemic control: HbA1c decreased from 8.08 ± 1.52% to 6.68 ± –1.07 (mean difference –1.39%; $P=0.000$) and FG from 169.4 ± 55.9 to 131.5 ± 38,2 mg/dl (mean difference –37.9; $P=0.000$). 28% of patients had a HbA1c < 7% in the beginning and 63% after 6 months of treatment with semaglutide. Baseline HbA1C was an independent predictor to achieve HbA1c < 7% 6 months after starting Semaglutide (OR 0,5; CI95% 0.31 to 0.81).
Table 1 shows the changes in anthropometric measurements.

Table1 Anthropometric measurements.

	Baseline	6 months after (mean difference)	P
Body weight (kg)	99.46 ± 18.87	94.11 ± 18.09 (–5.34)	0.000
BMI (kg/m^2)	36.14 ± 5.96	34.19 ± 5.5 (–1.95)	0.000
Waist circumference (cm)	118.2 ± 12.95	111.98 ± 14.36 (–6.22)	0.000
Fat mass (%)	42.46 ± 7.65	40.8 ± 8.5 (–1.58)	0.162
Muscle mass (kg)	30.65 ± 7.36	29.74 ± 6.12 (–0.91)	0.385

Conclusions
PwT2D in our clinic treated with Semaglutide (mostly 0.5 mg/week) for 6 months had a significant decrease in HbA1c, FG, body weight and waist circumference. The percentage of patients with HbA1c < 7% almost doubled.

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AEP463

Study on hypoglycemic effect of polyphenolic compounds isolated from the Euphorbia L. plants growing in uzbekistan

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Members of the *Euphorbia L.* genus have been used both in both traditional and alternative medicine for treatment of a wide range of disorders since time immemorial. Due to a wide spectrum of compounds of phoyphenolic nature, they are known to show anti-oxidant, anti-inflammatory, antimicrobial, fungicidal and antileukemic effects. The work was initiated to study a hypoglycemic effect of polyphenolic compounds isolated from two types of the Euphorbia L. genus. Polyphenolic compounds isolated from various organs of *Euphorbia ferganensis* (euphobin-1) and *Euphorbia franchetii* (euphorbin-2) growing in Uzbekistan were the objects for the study. Experimental diabetes mellitus was induced in rats by means of multiple administration of a diabetogenic dose of alloxan. Blood glucose reaching 11–12 mmol/l in 10–12 days, optimal dose of euphorbin was administered intragastrically every day for 10 days. Effect of euphorbin on the carbohydrate and lipid metabolism in blood and tissues of animals with experimental diabetes was compared to the one produced by quercetin, a polyphenol, and gliclazide, an antihyperglycemic agent. Optimal dose of euphorbin administered to animals with the induced alloxan diabetes was found to cause blood glucose decline from 12.0 to 8.1 mmol/l; the glycated hemoglobin reduced by 28%, while glycogen in the liver tissue increased by 14%. In rats with alloxan diabetes, the hexogenase activity in the muscles of the animals and the glucokinase activity in the liver could be seen. Euphorbin compounds, those of euphorbin 2, in particular, were found to decrease bloodcholesterol, triglycerides and low density lipoproteins by 29, 35 and 18%, respectively, alongside with the increase in high density lipoproteins and lipase activity to the control values. Thus, the hypoglycemic effect produced by euphorbin formulations and quercetin is believed to be determined not only by their influence on the β-cells of pancreas when viable β-cells undertake functions of the damaged ones (Sedigheh Asgary *et al.*, 2012), but also by partial restoration of carbohydrate and lipid metabolism in the tissues of rats with alloxan diabetes.

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AEP464

The effectiveness of glucagon-like peptide 1 receptor agonist and prebiotic on short-chain fatty acids and carbohydrate metabolism in patients with carbohydrate metabolism violation

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Background
Short-chain fatty acids (SCFAs) are organic fatty acids produced in the distal gut by bacterial fermentation of macrofibrous material. SCFAs play an important role in health and disease. They may reduce the risk of inflammatory diseases, type 2 diabetes, obesity, heart disease and other conditions.
Aims
to examine the effectivenessof glucagon-like peptide (GLP)-1 receptor agonist and prebiotic treatment on SCFAs, carbohydrate metabolism in patients with carbohydrate metabolism violation.
Materials and methods
In study were enrolled 19 patients with carbohydrate metabolism violation. The mean age of patients was 47 (30–60) years old. The levels of SCFAs, serum fasting glucose, glycated hemoglobin (HbA1c), and body mass index (BMI) were examined at baseline and at 12 weeks on therapy.
Results
At baseline the average glucose levels were 7,31 [5,6; 15,2] mmol/l, HbA1c – 7,2 [4,9; 9,9]%; and BMI – 39,8 [32,1; 51,0] kg/m^2. Significant positive relationship between acetate and HbA1c ($r(s)=0.34$; $P=0.022$), propionate and glucose ($r(s)=0.2$, $P=0.034$), and negative relationship between butyrate and BMI ($r(s)=–0.36$, $P=0.017$) were revealed at baseline. Patients in the GLP-1 and prebiotic therapy groups had a significant decrease in BMI, HbA1c and acetate after 12 weeks, with the mean decrease being 5.1 [1.4; 9.7] kg/m^2, 2.7 [1.0; 3.1]%; 2.34 [1.4; 2.9] mg/g ($P<0.01$), respectively. After therapy significant increase the level of butyrate: +0.6 [0.3; 0.6] mg/g ($P<0.01$).
Conclusions
The preliminary results are indicating a positive effect of GLP-1 and prebiotic therapy on weight, carbohydrate metabolism and short-chain fatty acids in patients with carbohydrate metabolism violation.

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AEP465

Adherence with lipid treatment guidelines in Swiss patients with diabetes mellitus – results from the SwissDiab study

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Introduction
The major cause of death and disability in patients with diabetes mellitus is atherosclerotic cardiovascular disease (ASCVD). Therefore, treatment guidelines specify strict target lipid levels for these patients. The aim of this study is to evaluate the adherence of diabetes mellitus type 1 and 2 patients (DM1 and DM2, respectively) with respect to the European and Swiss lipid treatment guidelines (ESC/EAS and AGLA, respectively).
Methods
The Swiss Diabetes Registry (SwissDiab) is a multicenter prospective observational cohort study of patients with diabetes treated at Swiss tertiary centers. Participants with DM1 and DM2 and a visit between 01.01.2018 and 30.09.2019 were included. Achievement of the LDL-cholesterol targets defined by the 2016 ESC/EAS and 2018 AGLA guidelines was assessed. Baseline characteristics as well as lipid-lowering medication were assessed stratified by diabetes type and in secondary analysis also by adherence to the respective guidelines.
Results
Overall, 187 participants with DM1 and 260 with DM2 were included. The ESC/EAS and AGLA LDL-cholesterol targets were met in 38% of DM1 participants and in 36% of DM2 participants. Among participants that did not reach the LDL-cholesterol targets based on the ESC and AGLA guidelines, 69% with DM1 and 26% with DM2 were not prescribed lipid-lowering medication. No difference in baseline characteristics, diabetes duration and HbA1c was observed between participants that reached and did not reached the LDL-cholesterol targets, regardless of diabetes type.
Conclusion
The proportion of SwissDiab participants with DM1 and DM2 that reach the LDL-cholesterol treatment targets is poor (<40%), consistent with previous studies showing that 20–40% of patients at high risk of ASCVD, such as DM patients, fail to reach established lipid treatment targets. The majority of DM1 patients that do not reach the LDL-cholesterol targets are not prescribed any lipid-lowering medication, suggesting that initiation of any lipid-lowering treatment would improve adherence to the lipid guidelines. The majority of DM2 patients do not reach the LDL-cholesterol targets despite being prescribed lipid-lowering medication, suggesting that combination lipid-lowering therapy should be reinforced to improve adherence to the lipid guidelines. In summary, our data strongly support that lipid-lowering strategies including high-dose statins and combination lipid-lowering treatments must be reinforced in Swiss patients with diabetes. The need is even more pressing in light of the more stringent 2019 ESC/EAS lipid guidelines in order to follow current recommendations and provide patients with the full benefits of these therapies.

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AEP466

Effectiveness of PCSK9 inhibitors in familial hypercholesterolemia in asturias, spain

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Introduction
Familial hypercholesterolemia (FH) is a genetic disorder characterized by high levels of LDL cholesterol (LDL-C) from birth. Treatment with statins and ezetimibe achieves in most cases large reductions in LDL-C. In those patients in whom the reduction in LDL-C is insufficient or who have intolerance to such treatments, the appearance of PCSK9 inhibitors has been an effective and safe alternative to achieve the LDL-C objectives.
Materials and methods
The results of the lipid profile of patients with FH treated with PCSK9 inhibitors in healthcare areas IV and VII of Asturias (Spain) were retrospectively analyzed. The indications for its use are those included in the consensus document of the Spanish Society of Atherosclerosis (2016).
Results
Data were obtained from 46 patients with FH treated with PCSK9 inhibitors, with a mean follow-up of 20.6 months. The average age was 59.13 years, with a similar distribution by sex (52.2% male).

Table 1 Evolution of medians of total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C) and triglycerides (TG) at the beginning of treatment, 2, 6, 12 and 24 months.

	TC (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	TG (mg/dl)
Initial	264,5	189	45	124
2 months	139	67	47	115
6 months	160	75	46	111
12 months	159	75	50	102,5
24 months	165	80	51	103

Table 2 Evolution of TC, LDL-C, HDL-C and TG at the beginning of treatment, 2, 6, 12 and 24 months expressed as a percentage.

	TC	LDL-C	HDL-C	TG
2 months	– 47,45%	– 64,55%	+ 4,44%	– 7,26%
6 months	– 39,5%	– 60,32%	+ 2,22%	– 10,48%
12 months	– 39,89%	– 60,32%	+ 11,11%	– 17,34%
24 months	– 37,62%	– 57,67%	+ 13,33%	– 16,94%

Conclusions
PCSK9 inhibitors are an effective treatment alternative for patients with FH. Although its maximum effect is achieved 2 months after the start of treatment, its effect is maintained at 2 years, with LDL- C reductions of more than 55%. Likewise, there is a slight increase in HDL-C and a moderate decrease in TG.

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AEP467

Outcomes of long pouch roux-en Y gastric bypass (LPRYGB): 4-years experience in primary and revision cases

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Background
One of the most important complications of the One Anastomosis Gastric Bypass (OAGB) is enterobilioacid reflux (EBAR). We report the concept of the Long Pouch Roux-en Y Gastric Bypass (LPRYGB) meaning a Roux-en-Y with a long pouch and a 100 cm alimentary limb to avoid EBAR, with a long biliopancreatic limb to increase metabolic effects.
Methods
A total of 300 LPRYGB cases in a four-year period, with a 90% follow up rate, were analyzed. Anthropometric, technical feasibility, morbidity, weight loss and comorbidity outcomes were analyzed.
Results
The percentage total weight loss (%TWL) was 30.5% at 4 years of follow up (32.3% in primary and 28.3% in revisions). Six intra-operative (2%) and 28 post-operative complications (9.3%) were seen. Out of this 28 complications 11 (3.6%) were late complications. Reoperations were performed in 15 patients (5.0%). Clinically relevant EBAR was present in 3 cases only (1%) 4 years after the operation.
Conclusions
The LPRYGB combines the main advantages of the OAGB (light restriction and moderate malabsorption) with the anti-reflux effect from the Roux-en-Y diversion.

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AEP468

The relationship between estradiol and obesity in men

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Introduction
Obesity increases the incidence of hypogonadism in men, and hypogonadism in turn plays a role in obesity. One of the first mechanisms proposed to explain this was a hypothesis based on the principle that obese men have higher estrogen levels, and that increased estrogens provide feedback to the hypothalamic-pituitary-testicular axis, reducing the secretion of gonadotropins and leading to a decrease of overall testosterone levels. This concept has since been questioned, though never completely disproven.
Methods
A total of 224 healthy men (except for their obesity) aged 20 to 78 with a broad range of body mass index (BMI) from 18 to 39 were enrolled in the study. All patients signed informed consent forms before taking part in the study. Blood withdrawal and anthropomorphic data were obtained from fasting subjects in the morning between 7:30 and 8:30 am. Serum total testosterone and estradiol were determined by radioimmunoassay. SHBG, lutropin and follitropin were measured using immunoradiometric assay. Moreover, we have calculated free testosterone. The men were then divided into three subgroups according to BMI. The first subgroup consisted of 109 men with BMI between 18 and 25 (normal weight men), the second group included 78 men with BMI between 25 and 30 (considered overweight), and the third subgroup had 37 men with BMI 30 to 39 (considered obese). We compared hormone levels betwen groups.
Results
The differences in estradiol levels between the groups were not significant. Though there was a relative increase of 10% in the levels of estradiol in obese men compared to normal weight men. In the overweight group there was even a decrease compared to normal weight men. In comparison with normal weight men, obese and overweight patients had significantly lower levels of total testosterone and higher SHBG, and in consequence the free androgen index. Total testosterone differed significantly between overweight and obese men, whereas SHBG differed significantly between normal weight men and overweight men, but not between overweight and obese men. Levels of FSH and LH showed no significant differences among the groups, though there was a slight tendency toward higher levels in obese men.
Conclusion
Our findings are in line with the idea that estrogen production in overweight and obese men with BMI up to 39 kg/m^2 does not significantly influence endocrine testicular function.
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AEP469

Role of biochemical indices in the pathogenesis of metabolic syndrome

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The defeat of the metabolic syndrome (MS) of young people with the development of severe vascular and diabetic complications determines the relevance of its study for the purpose of early diagnosis. Changes in blood at the preclinical stage of MS are reversible, while the main pathogenetic factors of MS are insulin resistance and dyslipidemia. The aim of the study was to assess the role of biochemical parameters in the pathogenesis of MS.
Materials and methods
50 MS patients and 35 healthy volunteers were examined. The glucose level was determined by the glucose oxidant method, the lipid profile was evaluated using standard test systems. Insulin levels were determined by enzyme-linked immunosorbent assay using a DRG test system. The method of chemiluminescence (CL) of neutrophils (NG) determined the time to reach the maximum (Tmax), maximum intensity (Imax) and the area (Smax) under the curve in the spontaneous and induced state. Statistical data processing was carried out using Statistica for Windows 8.0 application software packages with determination of median (Me) and interquartile range (C25-C75). The statistical significance of the differences was determined using the Mann – Whitney rank test $P<0.05$.
Results
In patients with MS, an increase in insulin and glucose levels was detected in the blood compared with the control group ($P<0.05$). Insulin resistance was evaluated by HOMA, in patients with MS revealed a two-fold increase ($P<0.05$). In most patients with MS, the level of triglycerides was within normal limits, only 40% of patients showed an increase in total cholesterol ($P<0.05$), in 100% of patients increased unesterified fatty acids (NEFA) ($P<0.05$). NG CL values were increased: Tmax, Imax, Smax, which indicates the activation of free radical oxidation of blood cells in MS ($P<0.05$).
Conclusion
In patients with MS, a violation of tissue resistance to insulin was detected, which requires constant monitoring of glucose in the blood. Of the lipid profile, the most significant indicator is an increase in NEFA, which leads to a decrease in hepatocyte binding of insulin and the development of peripheral insulin resistance. An increase in free radical oxidation enhances oxidative stress in MS.

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AEP470

Sleeve gastrectomy with loop duodenal switch (Fixed common channel) – Modification of single anastomosis duodenoileal bypass with sleeve for diabesity: An Institutional experience

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Introduction
Biliopancreatic diversion with duodenal switch (BPD DS) is the most effective metabolic surgery, but accounts for<1% of metabolic surgeries performed Worldwide due to its technical complexity and severe malabsorption. Its loop modification, single anastomosis duodenoileal bypass with sleeve (SADI S) with 200–250 cm common channel, reduces malabsorption to some extent. But a 250 cm common channel appears to be shorter for Indian patients. 'Sleeve gastrectomy with loop duodenal switch (Fixed common channel) – SG LDS (FCC)' is a further modification of SADI S, with a common channel length of 300 or 350 cm to reduce malabsorption further, without compromising on metabolic efficacy.
Material and methods
Between November 2014 and December 2019, 146 patients underwent SG LDS (FCC). Outcomes of these patients were retrospectively analyzed from prospectively entered database.
Results
Out of 157 patients, 22, 13, 101 and 10 had common channel of 250, 300, 350 and varied lengths. Mean BMI was 45.29±7.58 kg/m^2. 50.96% patients were suffering from type 2 diabetes. Mean excess weight losswith 25 BMI cut off point was 74.04%, 99.75% and diabetes remission with HbA1C<6 cut off, was 80.6%, 90.9% at 6 months and 1 year intervals respectively, Protein malnutrition with albumin levels<3 g/dl, was 44.4% and 8.6% with 250 and 350 cm common channel length respectively. 30 day mortality was zero.
Conclusions
SG LDS (FCC) appears to be a very effective and safe surgery. Maintained long term weight loss and Diabetes remission were positively significant. Malabsorption risk is greatly reduced when common channel length is increased to 300–350 cm or more.
Key words
Single anastomosis duodenoileal bypass, loop duodenal switch, fixed common channel, SADI S).

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AEP471

Circulating steroid hormones and BMI in men

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Introduction
Previous studies reported significant associations of steroid hormones with anthropometric parameters including body-mass-index (BMI) and waist circumference, as well as with some metabolic parameters such as triglycerides.
Methods
48 reproductive age males (age 18–49) were included in the study (27 obese individuals, 12 persons with excess body weight, 9 normal weight controls). We have examined the association between circulating steroid hormones and BMI. Plasma levels of aldosterone, progesterone, DHEA-S, 17-OH, 11-desoxicortisol, 21-desoxicortisol, androstenedione, corticosterone, testosterone and cortisol were quantified by liquid chromatography-mass spectrometry (LCMS), which provides high precision and specificity in the low concentration range.
Results
We compared three groups and confirmed statistically significant difference in plasma 17-OH levels ($P=0.005$), androstenedione levels ($P=0.048$) and testosterone levels ($P=0.0003$). Negative correlations were observed between plasma 17-OH concentration and BMI ($r=-0.49$, $P<0.001$), plasma androstenedione and BMI ($r=-0.29$, $P=0.044$), plasma testosterone and BMI ($r=-0.66$, $P<0.001$)
Conclusion
17-OH, androstenedione and testosterone plasma concentrations were negatively associated with BMI in men of reproductive age. Testosterone deficiency in obesity is well known and is due to aromatization in adipose tissue. Low 17-OH and androstenedione in obesity may reflect the influence of adipose tissue on steroid metabolism as well as on adrenal steroid production.

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AEP472

AKR1D1 regulates androgen availability *in vitro* by generating metabolites that are unable to activate the androgen receptor

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Introduction
AKR1D1 is a 5β-reductase that sits at the interface of steroid hormone metabolism and primary bile acid biosynthesis. 5β-reduced androgens are widely believed to be inactive, but to our knowledge there are currently no data that have directly tested their ability to activate the androgen receptor (AR). We therefore wanted to test the ability of AKR1D1 to regulate androgen availability *in vitro* and to determine if 5β-reduced androgens are able to activate the AR.
Methods
Human embryonic kidney cells (HEK293), that do not express AKR1D1, were transfected with either empty vector (EV) or AKR1D1. Cells were

treated with testosterone (T), 5α-dihydrotestosterone (5α-DHT), androstenedione (A4) or 11-ketotestosterone (11-KT) (all 200 nM) for 24 h. Media was collected for further analysis. Testosterone clearance was determined using a commercially available ELISA assay. The ability of androgens, their 5β-reduced metabolites, and the collected media from the AKR1D1 overexpression experiments, to activate the AR was determined using HEK293 cells co-transfected with AR and an ARE-luciferase construct.
Results
Successful AKR1D1 overexpression was confirmed using qPCR and Western Blot analysis. AKR1D1 over-expression increased T clearance ($P<0.001$). Using the AR/ARE co-transfection system, T and 5α-DHT were able to activate the AR. In contrast, 5β-DHT was inactive. In experiments using the conditioned media, AKR1D1 overexpression significantly reduced the ability of T, A4 and 11KT to activate the androgen receptor ($P<0.003$, $P<0.02$ and $P<0.007$, respectively).
Discussion and conclusion
We have demonstrated that 5β-reduced androgens are unable to activate the AR. In addition, we have shown that AKR1D1 clears androgens, including T, A4 and 11KT, and therefore has a potent role to regulate androgen availability and action. AKR1D1 is highly expressed in the liver, and it is dysregulated in diabetes and NAFLD. Alterations in androgen availability as a consequence of changes in AKR1D1 activity and expression, may be crucial in the pathogenesis of NAFLD.

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AEP473

Refeeding syndrome – an unexpected clinical case

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Refeeding syndrome can be defined as the potentially fatal shift in fluids and electrolytes that may occur after the reintroduction of feeding after a period of starvation or fasting in malnourished patients. The hallmark characteristic of refeeding syndrome is hypophosphatemia. However, the syndrome is complex and may also feature abnormal sodium and fluid balance, changes in glucose, protein and fat metabolism, hypokalemia, hypomagnesemia and thiamine deficiency. The underlying mechanism of this condition rests on the rise of insulin levels caused by refeeding, promoting cellular glucose and phosphorus uptake, leading to a sharp decline in serum phosphorus concentrations. Chronic alcoholics, elderly people, oncologic and anorectic patients are at higher risk of developing this condition. The authors report the case of a 54-year-old woman with history of *anorexia nervosa* and chronic alcoholism admitted with acute alcoholic hepatitis. On admission her body mass index (BMI) was 14,5 kg/m^2, and she started nutrition based on hospital culinary diet with enteric supplementation, adding up to a total intake of 2520 to 2720 kilocalories (Kcal) per day. On day 5 at the ward, the patient developed neurologic symptoms and signs consistent with Wernicke encephalopathy. Soon she developed shock with hypotension, and respiratory failureleading to inotropic support and mechanic ventilation. While in the intensive care unit, blood tests revealed severe hypophosphatemia, hypomagnesaemia, hypokalemia and thiamine deficiency. Other causes of shock, such as infection, pulmonary thromboembolism, acute coronary syndrome or structural heart disease, were excluded. Parenteral phosphate, thiamine, magnesium and potassium were administered and feeding was restarted at a slower rate. Her electrolytes normalized and she gradually improved and was discharged after 30 days with a caloric intake of 1000–1200 Kcal, motivated to maintain a progressive weight increase. This case illustrates the vulnerability of malnourished patientsto refeeding syndrome. Although it is necessary to combat malnutrition, the process of refeeding should be cautious. Measures should be taken to identify the risk of refeeding syndrome and prevent this potentially fatal condition.

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AEP474

Clinical analysis of three families caused by mitochondrial DNA mutation A3243G

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Maternally inherited diabetes and deafness (MIDD) is a rare form of diabetes caused by a mitochondrial DNA mutation. The condition is maternally inherited as mitochondrial DNA is practically only derived from oocytes. Patients typically have progressive insulinopenia, sensorineural hearing loss and maculardystrophy. We reported here 3 mitochondrial diabetes (two females and one male) and their families. Both of the 3 patients had diabetes, progressive loss of motor skills and sensorineural hearing loss. The average age of onset for diabetes was 34 years oldand the mean disease course was 16 years. At the beginning, they were all diagnosed as type 2 diabetes. After an average of 16 years, they were finally diagnosed as MIDD. The genetic testsshowed they all had A3243G mitochondrial DNA mutationwith different variation frequencies (12.80%, 25.00% and 13.95%, respectively). Besides, the third patient also had T16189C mitochondrial DNA mutation. Diabetes were non-insulin dependent at onset, but on average of 3 years later they started insulin therapy. In addition, patient 1 had suffered from headache for 1 month. A brain magnetic resonance imaging revealed cerebral infarction in left occipital lobe (subacute stage). So she also combined with MELAS (mitochondrialmyopathy, encephalopathy, lactic acidosis and stroke) syndrome. She has two daughters. The younger daughter was 20 years old and she had suffered from hearing loss for 1 year. She had the same mutation with her mother. But the genetic test of the asymptomatic older daughter was normal. The second patient's daughter and sister carried the same mutation with differentvariation frequencies (77.15%, and 5.12%, respectively). But her parents and brother were normal. The third patient's sister also suffered from diabetes and hearing loss when she was 23 years old. But she died of stroke at 30 years old. So we guessed that shesuffered from MIDD and MELAS syndrome. Even though this disease is maternal inheritance, but not all the people in this case follow the rule. It's partly due to the diverse levels of mutated mtDNA in different tissues. The identification of monogenic forms of diabetes is difficult. However, this condition should be considered when a history of diabetes associated with both hearing loss and relevant family history.

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AEP475

Descriptive analysis of body composition and phase angle (PA) in achondroplastic patients: Case-control study

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Introduction
Data on body composition in patients with achondroplasia are scarce. The Phase Angle (PA) is a bioelectric measurement of our body cells. The PA is considered to be a global prognostic factor that gives information about cellular function in relation to body composition.
Objectives
To describe body composition parameters PA, standardized PA (sPA), resistance (Rz), reactance (Xc), body cell mass (BCM), total body water (TBW), fat mass (FM), fat free mass (FFM) in a group of patients diagnosed with achondroplasia compared with controls paired by age and sex.
Material and methods
Observational study of 33 subjects (24 patients with achondroplasia and 9 controls). Bioimpedanciometry (by using AKERN 101 equipment) as well as anthropometric, nutritional and analytical data were collected.
Results
Body composition parameters were significantly different between achondroplastic patients and the control group. PA values were significantly lower in achondroplastic patients than in controls (5.3±0.1 deg vs 6.5±0.7 deg, respectively; $P=0.001$) as well as sPA (+0.9±0.8 vs –1.1±1.5 deg; $P=0.001$). Other body composition measurements are detailed in table 1. In addition, the sPA significantly correlated with PA ($r=0.930$), Xc ($r=0.873$), BCM ($r=0.646$) and height ($r=0.515$).

Table 1

Achondroplastic Patients ($n=24$) Mean (Standard deviation)		Controls ($n=9$) Mean (standard deviation)	P
Age (years)	14.3 (1.6)	14.0 (1.9)	0.655
Weight (Kg)	36.1 (8.5)	57.7 (12.4)	0.000
Height (cm)	123.3 (9.3)	164.7 (7.5)	0.000
FFM (Kg)	30.5 (5.2)	45.7 (7.1)	0.000
TBW (L)	25.6 (3.6)	32.7 (5.5)	0.000
BCM (Kg)	15.0 (3.1)	26.2 (4.7)	0.000
FM (Kg)	5.6 (5.4)	12.0 (7.8)	0.012
PA (deg)	5.3 (1.0)	6.5 (0.7)	0.001
sPA (deg)	−1.1 (1.5)	+0.9 (0.8)	0.001

Conclusions
There are relevant differences in the crude and standardized phase angle between the achondroplastic and healthy populations, adjusted for age and sex. These differences are related to a lower cell mass (BCM, FFM) and less clearly with water (TBW) and fat depots (FM).

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AEP476

A comparative analysis of the impact of the filipino plate method 'Pinggang Pinoy' vs standard nutrition education on food group proportions and 2-hour postprandial blood sugar levels of filipino diabetes patients

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Objectives
To assess whether nutrition education via the Filipino Plate Method 'Pinggang Pinoy' will be effective in developing better meal planning skills and 2-Hour Post Prandial Blood Sugar levels (2h-PPBS), comparable to standard nutrition education as recommended by the ADA.
Research design and method
The Filipino Plate Method 'Pinggang Pinoy' is a simple tool for nutrition advise and would only take approximately 15 minutes to teach as compared to the Standard Nutrition Advise which is more complicated and take as long as 90 minutes to teach. We enrolled a total of 148 Type 2 Diabetic subjects, with 113 participants (76%) completing up to the 2-Hour Post Prandial Blood Sugar levels (2 h-PPBS) determination. The participants were divided into two groups, wherein baseline knowledge were gathered. After which they received two sets of lectures one being The Filipino Plate Method and the other group receiving the Standard Nutrition Advise. Post teaching assessment for both groups were done after 3–6 days, in which they have undergone the same process of data collection. The Post Teaching scores from the Pre Teaching scores were compared based on 3 parameters: Meal Planning Drawing scores, Actual Meal Scores and 2-Hour Post Prandial Blood Sugar levels (2 h-PPBS) results.
Results
Interms of the actual plate scores, wherein overall score significantly increased from pre-teaching to post-teaching, and within both groups ($P<0.001$). Across groups, the Filipino Plate method group had a higher median score of 8/9 compared to 9/9 for the general education group ($P=0.018$). In terms of meal planning scores, the overall score significantly increased from pre-teaching to post-teaching, and within both groups ($P<0.005$). Across groups, the post-teaching scores were similar with a median of 5/10 ($P=0.274$). On baseline and on post-teaching, the 2 h-PPBS absolute values were significantly higher for the general education group compared to Plate method group. Scores remarkably decreased from baseline to post-teaching. However, the relative change, had insufficient evidence to demonstrate a statistically significant difference in 2 h-PPBS values between the two groups.
Conlusion
The Filipino Plate method 'Pinggang Pinoy' may improve meal planning skills, actual meal choices and proportions and may improve 2-Hour Post Prandial Blood Sugar, and maybe comparable to the Standard Nutrition Advise in patients with Type 2 Diabetes.

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AEP477

Comparison of basal metabolism rate assessment in athletes using indirect calorimetry, bioimpedance, and wearable monitors

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Wearable physical activity monitors are growing in popularity as they provide the opportunity for self-monitoring, real time data collection and data sharing for cardiovascular and sports medicine. However, there are discussions about the accuracy of their energy expenditure estimate. This study examined and compared basal metabolic rate through indirect calorimetry and through wrist-worn devices and bioimpedance. The group consisted of 30 healthy male individuals, professional football athletes, the age ranged from 20 to 38 years (26.81±4.78 years). Basal Metabolic Rate (BMR) data from the FitbitIonic collected during the protocol were compared with RJL System Bioimpedance and Indirect Calorimetry Cosmed. Anthropometric measures, body composition, and laboratory data were also observed. Spearman correlation and Mann-Whitney tests were used to calculate differences and correlations to examine associations between kcals measured from the Fitbit and bioimpedance from indirect calorimetry. Basal metabolic rate was 1824 kcal to 3504 kcal (2620.75±424.79). Results indicate significant ($P<0.001$) underestimations of kcals for Fitbit Ionic (1771±111,64). Moderate correlations were observed for the Fitbit and bioimpedance data. Body composition seems to influence Fitbit results, but hormonal status or anthropometric and physical findings were not associated to them. These findings support that caution is necessary when incorporating wearable devices BMR data, especially with weight reducing goals

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AEP478

Effectiveness of the low-calorie diet and exercise as an adjunct to the orlistat for the sustained change in metabolic parameters in young patients with type 2 diabetes with obesity

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Introduction
Obesity is a multifactorial disease which poses a serious public health problem, with an alarming epidemic character. The increase in bodyweight is associated with an increased risk of excessive fatrelated metabolic diseases including diabetes

Methods
We conducted an observational study to evaluate the clinical effects of orlistat in obese patients (BMI≥30 kg/m^2), adhering to low calorific diet limited to 1000–1100 kcal per day, moderate aerobic exercise of at least 150 minutes per week. We evaluated 100 consecutive patients during four visits (4, 6 and 12 months) over one year (June 2018–May 2019) in age group 21–40 years, adherent to orlistat 120 mg thrice daily. Educational interventions for the importance of the healthy lifestyle were provided periodically. The study was approved by the institutional ethics committee. ANOVA and unpaired t-test was used for the statistical analysis
Results
The mean age was 27.8 years (S.D.±8.51), with 46% less than 30 years. The mean baseline weight (kg) and HbA1c (%) was 88.7 (S.D.±14.06) and 8.2 (S.D.±2.11), respectively, which reduced to 68.02 (S.D.±10.29) and 6.3 (S.D.±1.15); $P<0.001$. The patients ($n=34$) with the lowest calorie intake (1000–1100 kcal/day) and with highest duration of exercise (>75 minutes per day) ($n=14$) achieved the maximum weight loss of 28.92 and 28.71 kg, respectively ($P=0.006$ and 0.001). The mean reductions at 4, 6 and 12 months in the body weight and HbA1c compared to baseline were 6.3, 14.5, 20.68 kg and 1.05, 2.17, 1.95% respectively ($P<0.001$)

Discussion
We observed a direct relationship for the benefits for the weight loss associated with the daily duration of exercise and the inverse relationship for the weight loss and calorie intake. Sustained lifestyle management as an adjuct to the orlistat therapy in young patients with T2DM, provides favorable benefits for the glycemic and metabolic parameters which may be attributed to improved adipocyte function and may go beyond the efficacy in weight reduction. The results of our study need to be corroborated with a large multi-centric trial

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AEP479

The effect of demographic factors on obesity in children (COSI project 2019), preliminary results

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Introduction
Demographic factors such as place of residence, urbanization grade and family background are considered to be associated with overweight and obesity in children. Our study investigates differences in obesity prevalence and related characteristics in children from urban, semi-urban, and rural areas, and in children from complete and incomplete families. The study is part of the fifth round of World Health Organization Europe's Childhood Obesity Surveillance Initiative (COSI)*.
Methods
We measured weight, height, waist and hip circumference in a representative sample of 2409 7-year-old Czech children in 2019. BMI was calculated from the data and the sample was classified using the WHO reference. Further health-related, behavioural and socio-economic information was gathered using family and school questionnaires. For the purpose of this analysis we evaluated a subsample of 1607 children. The association between dependent variables (place and urbanization grade of residence, family completeness) and a set of mutually correlated overweight/obesity predictors was evaluated using multivariate regression with a reduction of dimensionality, known as bidirectional orthogonal projections to latent structures (O2PLS).
Results
The urbanization grade of residential location appears to play a significant role in child obesity-related factors. In rural areas, more school playgrounds are available after school, children need to travel to school a longer distance but are less likely to walk to school. Children are also more likely to live with both parents, while in urban areas more families are single-parent. Neither BMI nor weight category was affected by the place of residence. The analysis revealed that children from complete families had significantly higher weight and height. This, however, did not translate into differences in BMI or weight category of the children, either.
Conclusion
Children from urban, semi-urban, and rural areas are exposed to different sets of obesity-related factors, as are children from complete and incomplete families. Family completeness also correlates with the children's weight and height. Yet no significant correlation was found between the urbanization grade, place of residence, or family background and BMI and the weight category in 7-year-old Czech children.
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AEP480

Investigating the role of olfactory receptors in endometrial cancer cells

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Laron syndrome (LS) is a rare autosomal recessive genetic disorder caused by growth hormone receptor (GH-R) gene mutations, leading to congenital insulin-like growth factor-1 (IGF1) deficiency and dwarfism. Epidemiological studies have shown that there are no LS patients that suffer from cancer, which means they are protected from cancer development. While the mechanisms associated with cancer protection in LS are unknown, cancer protection might involve the insulin (INS) and IGF1 signaling pathways. These hormones have been implicated in the etiology of several epithelial neoplasms and have a crucial role in endometrial cancer development.
To investigate the potential cancer protective pathways in LS patients, our laboratory has previously conducted genome wide transcriptome analyses (microarray analysis) using lymphoblastoid cell lines derived from LS patients and healthy controls. The olfactory receptor (OR5H2) gene was among a group of genes shown to be differentially expressed in LS patients. The involvement of the OR5H2 gene in endometrial cancer biology is unknown. Furthermore, most of the differentially expressed genes, including the OR5H2, were not previously linked to IGF1 signaling.
The aim of the project is to evaluate the expression and regulation of the OR5H2 gene in endometrial cancer cells. In addition, we are interested in assessing the potential regulation of OR5H2 expression by IGF1 and insulin. The overall aim of my project is to elucidate the potential role of OR2H5 in endometrial cancer. Two endometrial cancer cell lines will be used in this project as Type II: Uterine serous papillary endometrial carcinoma type 1-derived and uterine serous papillary endometrial carcinoma type 2-derived (USPC-1 and USPC-2). Utilizing these two types of cells will let us examine also the P-53 effect on the regulation of the target gene, for the USPC2 cell line is P-53 mutant, whereas P-53 is wild type in USPC1 cell line.
Evaluation of OR5H5 basal expression levels in preliminary studies using RT-PCR showed differences in basal expression levels between the two endometrial cancer cell lines.

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AEP481

Nesidioblastosis a rare cause of hipoglycemia in adults

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Introduction
Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) is an entity with low prevalence (4%), more frequent in neonates and infants and with a male preponderance, characterized by endogenous hyper insulinemic hypoglycemia, not caused by an insulinoma. Pancreatic histology usually reveals diffuse nesidioblastosis.
Case report
A 21-years-old man without a remarkable personal or family history was referred describing a 15 kg weight gain and late-afternoon asthenia and drowsines for the last two years that improved eating carbohydrates. He also described several episodes of loss of consciousness and neuroglycopenic symptoms cooccurring with glycemia of 32 mg/dl despite nutritional modifications and diazoxide. Results of a fasting test showed: glycemia 42 mg/dl, plasma insulin 11.5 mcrUI/ml, C-peptide 2.35 ng/ml, proinsulin 1.5 pmol/l, low beta-hydroxybutyrate, a negative sulfonylurea/meglitinide screen and negative insulin antibodies and insulin-receptor antibodies. As an insulinoma was suspected, transabdominal ultrasonography, abdominal computed tomography (CT), magnetic resonance imaging (MRI), and a 99 m Tc somatostatin receptor scintigraphywere performed, with negative results. A selective arterial calcium stimulation test (SACST) with hepatic venous sampling after calcium gluconate infusion did not show any gradient.

	Superior mesenteric artery	Gastroduodenal artery	Splenic artery
Basal Insulin mcr UI/ml	19.50	21.30	19.10
Insulin 30 s mcrUI/ml	22.20	24.40	33.20
Insulin 60 s mcrUI/ml	35.90	35.30	48.30
Insulin 120 s mcrUI/ml	71.60	71.60	67.10

Due to persistent symptoms refractory to medical management and localization results a partial pancreatectomy was performed in which histopathology descriptions showed patchy nesidioblastosis changes, islet cell hypertrophy and redifferentiation of islet of Langerhans cells from pancreatic duct epithelium. After surgery patient´s symptoms greatly improved.

Discussion
The predominant clinical feature of noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) is usually postprandial hypoglycemia but also fasting hypoglycemia can occur, with biochemical findings similar to insulinoma. For patients with NIPHS and refractory postprandial hypoglycemia, surgery remains the mainstay of therapy.

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AEP482

Adherence to treatment in 102 tunisian adolescents with type 1 diabetes

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Background
Type 1 diabetes mellitus is the most common chronic illness in childhood. His treatment involves a multifaceted regimen that includes daily blood glucose monitoring, insulin injections, a dietary plan, and regular exercise. Patients, especially during adolescence, do not fully adhere to the diabetes treatment and, as a result, they appear to be at risk for serious medical complications, including hyperglycemic episodes, Ketoacidosis and microvascular complications such as retinopathy, nephropathy and neuropathy.
Aims
To assess adherence to treatment in a group of Tunisian adolescents with type 1 diabetes and study the consequences on the balance of diabetes
Methods
Cross sectional study concerning 102 adolescents with type 1 diabetes hospitalized or followed at the consultation of diabetology of the Institute of Nutrition in Tunis over a one-year period between January 2017 and January 2018. To assess adherence to treatment, we used the validated version in Arabic of the self-questionnaire derived from the Medication Adherence Questionnaire (MAQR) from Morisky-Green. This questionnaire contains 6 yes/no items. It targets memory and attention, as well as knowledge and opinion. It allows you to define three grip profiles:
– Good adherence if the answer is 'no' for the 6 items
– Moderate adherence if 1 or 2 'yes' answers
– Poor adherence if 3 or more 'yes' answers
Results
The study population consisted of 102 adolescents with type1 diabetes and 51% were female. The mean duration of diabetes was 7.1±4.3 years. The daily average of insulin dose was 1±0.4 u/kg/ day. The average number of injections per day was 3.4±1 with extremes ranging from 2 to 5 injections per day. Adherence to treatment was good in 12.8% of patients, moderate in 57,8% and poor in 29,4%. Insulin omission was present in 7.8%. The average rate of HbA1c was 10.6±2.2% with extremes ranging from 5.8 to 16.8%. Diabetic retinopathy, nephropathy, and neuropathy were found respectively in 3.9%, 5.9%, and 5.9%. The average number of ketosis or Ketoacidosis in the last year was 3,6±6,3 per year. severe hypoglycemia rate in the past 3 months was 1.8±7,9 per month.
Conclusion
Child routines and the complexity of diabetes treatment may influence behaviorally problematic youths 'risk for poor adherence to T1DM treatment. Clinicians and parents are encouraged to cultivate child routines early in development because it may reduce the risk for parent – child conflicts in adolescence, which can compromise the adherence to treatment.

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AEP483

Evolution of lipidic parameters in a population of patients with type 2 diabetes after switching on insulin analogs

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Introduction
The advent of insulin analogs has significantly reduced the undesirable effects of human insulin, particularly hypoglycemia. Beneficial effects on the lipid balance have also been described. The aimof our study was to describe the evolution of the lipidic parameters after the switch on insulin analogs.
Patients and methods
This is a longitudinal retrospective study about 61 patients with type 2 diabetes, switched to insulin analogs since at least 3 months. Clinical and biological data were taken from medical records. During the study, no modification or introduction of lipid-lowering therapy was made.
Results
The mean age was 60.7±10.2 years. The sex ratio was 0.96. Diabetes had evolved for an average of 18.1±8.9 years. Retinopathy and diabetic nephropathy were frequent by 49% and 41.7% respectively. The mean duration of insulin analog therapy was 17.33±10.13 months. Determir was the most prescribed slow insulin analog (59%). Insulin Aspart was the most widely prescribed rapid insulin analog (76.8%). 82% of the patients were hypertensive. 85.2% were dyslipidemic. The mean CT and LDL levels decreased significantly during the 3 periods studied (CT (T0)=4.9 mmol/l, CT at 3 months=4.63 (P=0.035), CT at 6 months=4, 45 (P=0.02), CT at one year=4.25 (P=0.017), (LDL (T0)=3.2 mmol/l, LDL at 3 months=2.98 (P=0.012), LDL at 6 months=2.75 (P=0.003), LDL at 1 year=2.5 (P=0.001) The HDL level remained stable The TG level increased without reaching the significance level. The percentage of patients achieving the LDL objective was maximum at 1 year (T0: 18.2%, at 3 months: 31.4%, at 6 months: 37.1%, at 12 months: 55.6%). The percentage of patients achieving the HDL target remained stable (T0: 33.3%, at 3 months: 31.4%, at 6 months: 33.3%, at 12 months: 33.3%). The percentage of patients achieving the TG target was maximal at 1 year (T0: 68.5%, at 3 months: 71.4%, at 6 months: 69%, at 12 months: 73%).
Conclusion
The modification of the lipidic parameters after switching to insulin analogs had been reported in the literature. It was linked, among others, to the weight change. Studies on a larger scale are essential in order to better characterize the variation in the lipidic balance after switching to analogs and to identify the associated factors.

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AEP484

Flash glucose monitoring system: Impact on glycaemic control and body mass index in type 1 diabetes mellitus

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Background
The use of Flash Glucose Monitoring (FGM) for the management of type 1 diabetes mellitus (T1D) is rapidly increasing.
Aims
To assess the longitudinal evolution of glycated haemoglobin (HbA1c) and body mass index (BMI) with the use of FGM in patients with T1D; to determine predictive factors of benefit with the use of this technology.
Materials and methods
Retrospective study of T1D patients, using FGM ≥6 months and treated with multiple daily doses of insulin. Patients whochanged the type of basal insulin, began/suspended oral hypoglycaemic drugs or were/became pregnancy during the analysed period were excluded.
Results
179 patients included, 52.5% males. The median age (Md) was 43.0 (P25 31.0; P75 52.0) years old, median duration of disease was 18.0 (P25 10.0; P75 28.0) years and 33.5% were treated with functional insulin therapy. The initial HbA1c was Md 7.9% (P25 7.2; P75 8.8); 49.1% with initial HbA1c≥8%. The initial BMI was 24.0 Kg/m^2 (P25 21.9; P75 26.2); 39% were overweight/obese. FGM usage time was 6 months in 25.7%, 12 months in 34.6% and ≥18 months in 39.7% patients. FGM was associated with a significant improvement in HbA1c during the first year, with Md HbA1c 7.6% (P25 7.0; P75 8.3) at 6 months and 7.7% (P25 6.95; P75 8.5) at 12 months (P<0.05). At 6 months, there was a significant increase in the number of patients with HbA1c<7% (16.1% vs 25.0%) and a significant reduction in the number of patients with HbA1c≥8% (49.1 vs 37.1%) (P<0.05). In multivariate longitudinal regression analysis, initial HbA1c 8.0–8.9% (HR 1.886; CI 1.321; 2.450) and ≥9.0% (HR 3.108, CI 2.454; 3.761) and initial BMI 25.0–29.9 kg/m^2 (HR –0.397; CI –0.793; –0.001) were predictors of greaterHbA1c reduction. BMI increased significantly during the 12 months follow-up, especially during the second 6 months, with BMI Md 23.8 (P25 21,9; P75 26,2) kg/m^2 and 24.0 (P25 22.0; P75 26.2) kg/m^2 at 6 and 12 months, respectively (P<0.05). In multivariate longitudinal regression analysis, initial BMI 25.0–29.9 kg/m^2 (HR 4.319, CI 3.185; 5.453) and ≥30 kg/m^2 (HR 8.112, CI 3.919; 12.306) were predictors of greater weight gain.
Conclusion
In the first year of FGM use, there was a significant improvement in HbA1c, mainly in patients with a previous worst glycemic control. When starting

FGM, weight control strategies should be considered, especially in overweight/obese patients.

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AEP485

Effect of ramadan's fastingon the glycemic balance of a diabetic population with an HbA1C before the fast greater than 10%

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Introduction
International recommendations prohibit fasting of the month of Ramadan in patients with diabetes, particularly unbalanced ones.
The aim of our study was to describe the evolution of the glycemic balance in unbalanced diabetics with an HbA1C before the fasting greater than 10%.
Patients and methods
This is a descriptive evaluative study carried out on 25 patients with type 2 and with an HbA1C before fasting greater than 10%. These patients were advised not to fast and the risks involved were explained to them. Then they had an education and a therapeutic adjustment by referring to the recommendations of the Amercian Diabetes Association (ADA)of 2016.
Results
The average age was 56.5 8.8 years with extremes of 35 and 70 years. The sex ratio was 0.62. The average duration of the progression of diabetes was 9±6.4 years. The average body mass index (BMI) was 28.8±6.1 kg/m^2 with extremes of 20.5 and 45.1 kg /m^2. 72% were overweight or obese. The days fasted were successive with an average of 20.3±9.6 days. (48% (n=12) had fasted for the entire month. After the fasting, HbA1C had increased from 10.26±1.58% to 10.78±0.92% after fasting (+0,52±1.7%, P=0.137). 19.2% (n=5) had hypoglycaemia motivating the cessation of fasting in 15.3% (n=4). 11.5% (n=3) had hyperglycemia justifying the end of the fast in all cases.
Conclusion
Fasting for the month of Ramadan should be strongly discouraged in very unbalanced diabetic patients given the risks involved, including hypoglycemia and glycemic imbalance.

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AEP486

Glycemic variability in type 1 diabetes

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Introduction
Glycemic variability (GV) is emerging as a measure of glycemic control in type 1 diabetic patients (T1DM) given that it provides an integrated picture of postprandial hyperglycemia and hypoglycemic episodes and is associated with diabetic complications and mortality. However, little is known about the best way to address this problem in clinical practice.
Aim
To characterize GV in T1DM patients followed in our center and to identify clinical predictors for higher GV.
Methodology
Retrospective cohort study, including adults with T1D diagnosed clinically for ≥12 monthsthat were using flash glucose monitoring (FGM) systems ≥70% of the time. Raw data fromFGMwas downloaded in each visit from July 1st 2018 to December 31st 2019, and two periods of 28 consecutive days were selected, for each patient, and analyzed the following parameters: % of time in range (TIR [70–180 mg/dl]), % of time below range (TBR [<70 mg/dl]), % of time below 55 mg/dl (TBR55),% of time above range (TAR [>180 mg/dl]), % of time above 250 mg/dl (TAR250) and coefficient of variation (CV). A cutoff threshold value of 36% for CV was assumed to separate stable from labile glycemic control.
Results
Inclusion of seventy-five T1DM patients (62.7% female), with mean age 46.7±13.5 years and mean duration of T1DM 25.4±13.3 years. Fifty (66,7%) patients were using CSII. Carb counting was used by 59 (78.7%) patients. Adjuvant therapy was used in 22 (29.3%) patients (21,3% metformin, 5.3% GLP-1 agonists, 4.0% DPP4- inhibitors and 4.0% SGLT2 inhibitors). Mean A1c was 7.6±0.9% and 18 (25.7%) patients had HbA1c≤7%. Microvascular complications were present in 38 (48.7%) patients (diabetic retinopathy in 45.3%, nephropathy in 24.2% and peripheral neuropathy in 17.3%) andmacrovascular complications in one (1.3%) patient. Median TIR/TBR/TAR were 49 (38–70)%; 5.0 (3–7.5)% and 44.5 (30.5–57.5)%, respectively. Nine (12%) patients with TIR>70% and 29 (38.7%) with TBR<4%. Mean CV was 41.2±7.3 reflecting labile control in 80% (n=60) patients. Vascular complications were more frequent in this group (58.3% vs 20%, P=0.01). Disease duration was associated with higher CV [OR: 1,28 (CI 95%: 1.03–1.60)] but neither age, sex, body mass index, carbs counting, CSII or adjuvant therapy showed to be predictors of GV in our sample.
Conclusions
GV was high in this sample and associated with longer disease duration, translating the difficulties that both patients and health care professionals face every day and reinforcing the need for strategies to reduce GV effectively.

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AEP487

Efficacy and safety of switching from a dipeptidyl peptidase-4 inhibitor to a glucagon-like peptide-1 receptor agonist: A real-world experience

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Introduction
Glucagon-like peptide-1 agonists (GLP1a) and dipeptidyl peptidase-4 inhibitors (DPP4i) are both incretin-based therapies for type 2 diabetes (T2DM) but with distinct efficacy according to glycemic and weight control and side effect profiles. There is scarce information about changes observed after switching from a DPP4i to a GLP1a in patients with T2DM on a complex treatment regimen and routine clinical practice conditions. To assess these changes, we carried out this study to analyze if there were any beneficial effects of switching from DPP4i to once-weekly dulaglutide (a GLP1a) in poorly controlled patients with T2DM. Safety of that switch was also evaluated.
Methods/Design
An observational and retrospective study was carried out in T2DM poorly controlled patients in routine clinical practice. Variables used to assess efficacy were changes in HbA1c, fasting plasma glucose (FPG) and weight from switching to week 12 to 20 (period 1) and week 21–36 (period 2). Additionally, changes in antidiabetic drugs to maintain adequate glycemic control were evaluated. Safety variables were: hypoglycemic events and side effects related to GLP1a.
Results
Data from 60 patients (age: 61.3±9.4 years; HbA1c: 8.6±1.3%; duration of T2DM: 13.4±8.4 years) were collected. 63.3% of the cohort was on insulin. A significant reduction (P<0.001) in HbA1c, FPG and weight was observed in both periods of follow-up: HbA1c: –1.39% (CI 95%: –1.7 to –1.1) and –1.37% (CI 95%: –1.6 to –0.9); FPG: –33.2 mg/dl (CI 95%: –61.4 to –16.7) and –34.6 mg/dl (CI 95%: –57.3 to –18.2); weight: 2.14 kg (CI 95%: –3.99 to –2.36) and –3.36 (CI 95%: –3.35 to –1.45). In patients on insulin, a significant reduction in insulin doses was observed only in the first period (–0.13 IU/kg; P=0.031). Any intensification of antidiabetic treatment was required in 7.8% and 30.9% of the cohort in period 1 and 2, respectively. At least, one hypoglycemic event (no severe) was described in 12.7% of the patients. No patients required withdrawal from dulaglutide during follow-up.
Conclusions
Switching from DPP4i to GLP1a (dulaglutide) in patients with T2DM, and routine clinical practice, of our cohort, resulted in sustained HbA1c, FPG and weight reductions without compromising safety.

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AEP488

Evaluation of the results obtained with flash continuous glucose monitoring in patients with type 1 diabetes after a structured training program

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Introduction
Funding of continuous glucose monitoring (CGM) has been established by Madrid Health Service for adults with type1 Diabetes Mellitus (DM) who meet specific criteria. This has brought to lightthe need foran increasedinvestment in care time. In our Division, a structured training program has been established, consisting of 2 training sessions (TS); the first one based on basic contents to initiateFlash-CGM, and the second one, more intensive and targeted, focused on the correct interpretation of the resulting data.
Aims
To evaluateglucose control of patients with type 1DM after undergoing a structured training program on theuse of Flash-CGM and toevaluatethe degree of patient satisfaction withtrainingitself, and regarding their management of DM.
Methods
Analysis of downloaded LibreView data of 50 patients using Flash-CGM. Description of demographic and analytical variables, and those related to glycaemic control provided by Flash-CGM system, after undergoing two TS separated in time. Descriptive and inferential statistics: SPSSv.25
Results
50 patients with type1 DM, 27 women, aged 39 [18–86], mean DM duration 20.76±12.27 years. Initial/previous/prior Hba1c: 7.3% [5.5–9.3%]. 5 used insulin pump and 21 were previous users of Flash-CGM. Number of scans/day:17 in pump-patients, 12 in patients on multiple daily injections. A decrease in mean HbA1c was noted with use of Flash-CGM (7.224 to 7.092%, $P=0.117$). No significant differences in glycaemic control adjusted for DM duration, gender, BMI, time using Flash-CGM or being on a pump were found between the two TS. We observeda decrease in the number of scans in non-previous users after the second TS (12.25±4.84 to 11.11±4.37, $P=0.021$). Younger users (≤39 years) reduced their number of scans after the second TS (13.16±5.71 to 11.04±4.12 ($P=0.001$). No significant correlation between the number of scans and time in range was found after the first TS. There was a significant correlation between the number of scans and time in range after the second TS (beta regression coefficient 0.371, $P=0.009$). Hypoglycaemic events and time in hypoglycaemia improved (15.75±16.30 (1st TS) to 13.57±6.8 (2nd TS) and 106.78±34.5 min (1st TS) to 104.59±37.98 min (2nd TS), (non-significant decrease). Patients showed a high degree of satisfaction (93% in DTSQ-c scale), better understanding of DM (95.4% DTSQ-c) and of glycaemic behaviour (93.3% EVA scale), and an overall high satisfaction (88.8%) with the training program received.
Conclusion
Flash-CGM increases time in range, HbA1c and quality of life. After the training program, satisfaction and understanding of glycaemic behaviour improve, denoting the importance of a continuous training process.

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AEP489

The association of vitamin B12 deficiency with metformin uses

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Introduction
Metformin is the first line treatment of type 2 diabetes, but now has been reported to cause a decrease in level of Vitamin B12.
The aim of the study is to describe the prevalence of vitamin B12 deficiency in adults with type 2 Diabetes Mellitus who were in treatment with metformin compared in those without diabetes.
Material and methods
Total number of patients were 130 between 16–84 years old. Mean age 54.2±16.4 years. Female were 56.9% (74 patients) and males 43.1% (56 patients). Serum B12 concentrations were quantified by chemiluminescent enzyme immunoassay. Patients were considered vitamin B12 deficiency if the level was less than 200 pg/ml and borderline-low B12 (≤300 pg/mL) they were in treatment with metformin over one year.
Results
The mean vitamin B12 level in all patients was 337.1±155.5 pg/ml. A total of 16.1% (21 patients) showed vitamin B12 deficiency with mean vitamin B12 level of 145.3±30.4 pg/m; and 48.4% (63 patients) showed borderline-low B12 with mean vitamin B12 level of 214±56.9 pg/ml. The mean concentration of B12 was significantly lower in the metformin treated group (264 pg/ml) compared to those without diabetes (409 pg/ml) ($P=0.06$). About 21.5% of persons with diabetes receiving metformin were vitamin B12 deficient (<200 pg/ml) compared to 4% of persons without diabetes.
Conclusions
Uses of metformin was associated with Vitamin B12 deficiency. Routine testing of vitamin B12 levels in metformin-treated patients should be considered and the clinician must be aware of the possibility of metformin-related B12 deficiency.

Keywords: Vitamin B12, metformin.
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AEP490

Clinical and safety profile of empagliflozin in nepalese type 2 diabetes patients

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Background
The only available SGLT2 inhibitor in Nepal till date is empagliflozin. Empaglilozin has shown to be cardioprotective and renoprotective in randomized trials. It has shown to reduce some weight. There is a lack of data of SGLT2 inhibitors in Nepalese Type 2 diabetes patients.
Aim
The aim of our study is to determine the effects of empagliflozin in glycemic control in terms of HbA1C reduction, weight, improvement in eGFR and side effect profile in Nepalese Type 2 diabetes patients.
Method
This is a retrospective study conducted in our OPD patients from February to September 2019 who were initiated on empagliflozin 10 mg per day who were already on other OHAs and/or insulin therapy. A total of 440 patients were prescribed empagliflozin out of which 230 patients came for the follow up at 3 months and 111 patients in 6 months. Hence, only the data from 111 patients who completed 6 months follow up were analyzed. 55.9% ($n=62$) patients were on insulin treatment.
Result
The findings of the study revealed that, out of 111 patients, 53.15% ($n=59$) were female and 46.8% ($n=52$) were male. Mean HbA1C at the time of initiation of empagliflozin was 7.9 (±1) % while it reduced to 7 (±1) % in 6 months. There was improvement in eGFR from 85 to 92 ml/min/1.73 m^2. There was weight loss from 71 (±13) kg to 68 (±11) kg at the end of 6 months. There were few incidence of genital infection. Notably, vulvovaginitis was observed in 15.25% of female patients ($n=9$), urinary tract infection in 5.4% of all patients ($n=6$), balanoposthitis in 3.84% of male patients ($n=2$).
Conclusion
There was improvement in glycemic control, weight loss and improvement in eGFR after initiation of empagliflozin in Nepalese Type 2 diabetes patients at the end of 6 months follow up.

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AEP491

The efficacy of dulaglutide in the treatment of patients with type 2 diabetes and NAFLD in real clinical practice

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Background
Dulaglutide has been approved as a hypoglycemic agent for the treatment of patients with T2DM. A positive effect on carbohydrate metabolism and body weight was shown in RCT.
It was found that GLP-1 agonists may prevent the progression of NAFLD directly affecting lipid metabolism and inflammation.
Aim
To assess the effect of dulaglutide on carbohydrate and hepatic metabolism in patients with T2DM and NAFLD in real clinical practice in Moscow Region.
Design
Open observational prospective cohort study of real clinical practice. After approval by LEC 45 pts with T2DM and NAFLD, BMI ≥ 27 kg/m^2, receiving basic therapy at the time of inclusion with daily dose of metformin ≥ 1,500 mg as monotherapy or as part of a combination therapy were condacted to the study with treatment of dulaglutide subcutaneus injections 1,5 mg weekly for 26 weeks. Mean age 55.6 ± 10.6 лет, 16(36%) men. All patients undergo physical examination withheight, weekly weight, waist and hip circumference measurement, monthly blood sampling tests (HbA1c, FPG, ALT, AST, GGT, lipids, hematology), ultrasound, elastometry using Fibroscan before and after 26 weeks of treatment. Also FIB4, FLI were calculated before and after 26 weeks of treatment. Statistical analysis was done using by MedCalc Version 19.1 using Wilcoxon test for nonparametric and Fisher test for parametric data. Results presented in median with interquartile range (IQR).
Results
In real clinical practice with weekly visits it was found statistically significant difference of weight loss. 5% weight loss was found in 56.0% pts, 10% weight loss – in 7.0% of patient, median weight loss was –5 kg in 26 weeks. A statistically significant decrease in weight, BMI, waist circumference, HbA1c, ALT levels was detected in the whole group, despite the fact that the goal of more than 5% of the initial weight loss have reached only 56,0% of patients. There was no statistical difference in hip circumference, FPG, AST, GGT, lipids levels. Median of HbA1c decreased from 7.4% (6.1–8.4) to 6,3 (5.6–6.8), ALT median decreased from 67.2 (IQR 35.5–96.9) to 38.2 (IQR 22.6–62.9). A downward trend in FLI and TE was also noted, although absolute values corresponded to a high risk of steatosis.
Conclusion
In real clinical practice Dulaglutide may have a positive effect on weight loss, metabolic and hepatic parameters in patients with NAFLD and T2DM.

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AEP492

Association of B12 levels with metformin use in type 2 diabetes patients

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Background
Metformin is the most widely used oral antihyperglycaemic drug, but it may lower B_{12} status, which could have important clinical implications.
Aim
To study serum Vitamin B_{12} levels in patients with type 2 diabetes mellitus who were receiving metformin and compared them to those never treated with metformin.
Materials and Methods
A total of 60 patients with type 2 DM (group 1, $n=35$, receiving metformin and group 2, $n=25$, never treated with metformin) from the endocrinology clinic in Chernivtsi were studied. Serum vitamin B_{12} levels were measured in all patients.
Results
The serum vitamin B_{12} levels were 239.6 ± 37.4 pg/ml in metformin group and 293.6 ± 42.3 pg/ml in the no metformin group ($P=0.37$). When adjusted for duration of DM, metformin use was associated with a 57.2 ± 7.3 pg/ml ($P=0.03$) lower serum vitamin B_{12} levels. Serum vitamin B_{12} levels were higher by 41.4 pg/ml in patients with DM of 1–5 years compared to those with recently diagnosed diabetes ($P=0.41$). Serum vitamin B_{12} levels were higher by 119.4 pg/ml in patients with duration of DM > 5 years compared to those with recently diagnosed diabetes ($P<0.02$). Similarly, serum vitamin B_{12} levels were 77.1 pg/ml higher in > 5 years DM duration group compared to 1–5 year duration of DM group ($P=0.03$). Serum vitamin B_{12} levels for the entire cohort were higher by 11.8 ± 1.7 pg/ml ($P<0.01$) for every 1 year increase in the DM duration.
Conclusions
Metformin use was associated with a lower serum vitamin B_{12} levels when adjusted for duration of DM. Increasing duration of DM was associated with higher serum vitamin B_{12} levels.

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AEP493

Insulin usage and injection practices in a largeIndian cohort: An audit

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Objective
Despite an increase ininsulin utilization in India over the past 10 years, wide variation exists in injection practices and usage across the Indian geography. This cross-sectional study was designed to audit various aspects of insulin usage, tolerability and efficacy of insulin regimens, degree of variability in injection techniques and its causes, interactions, and associations with glucose control and other outcomes.
Methods
Data for this cross-sectional retrospectivestudy was collected from the prescription registry of an electronic database including consecutive patients attendinga private urban referral clinic from North Eastern India between January 2006 until December 2016. T2DM patients using insulin for more than 3 months and having aninitial HbA1c level at registration were included. Information on patient demography, HbA_{1c}, insulin injection practices (including injection site, rotation, needle reuse, and lipohypertrophy), self-monitored blood glucose, and hypoglycemic events in the past 6 months were collected.
Results
Data of 1454 patients with T2DM (60.38% male, mean age 54.63 ± 10.79 years, range 18–85 years) on median duration of insulin therapy for 2.00 (0.0: 37) years were collected. Mean dose of insulin was 33.1 ± 17.8 units/day. Majority were taking human insulin (61.21%) andt he rest (34.59%) were on insulin analogues. Premix insulin (67.88%) was the most common type of insulin used followed by basal insulin (10.90%), basal bolus (6.50%), bolus only insulin (6.33%) and combination of premix with bolus (5.7%). 62.53% used pen device. OAD failure (33.15%), glucotoxicity (30.26%), and diabetic complications (20.36%) were prominentindications for starting insulin. Mean HbA1c(%) was 9.2 ± 2.2. Less than 16% of patients had HbA1c < 7%. Faulty injection practices were underscored by improper rotation of injection sites (67.61%) and needle reuse (73.11%). Majority followed right practices w.r t. storage (65.13%), hygiene (82.1%), correct site and angle for injection (78.4% and 81.84% respectively). Visible or palpable Liohypertrohy (LH) was found in 12.38% of subjects which was significantly associated with wrong rotation and needle reuse. Hypoglycemic events were insignificantly associated with type of insulin, or various attributes of insulin injection practices.
Discussion
This study, in spite of inherent limitations, convincingly shows that metabolic control remains poor amongst patients using insulin. Wrong injection practices, resultant LH and inadequate dose may be contributory.
Conclusion
There are identifiable faulty injection practices amongst T2DM patients on insulin, and therapeutic inertia amongst prescribing physicians which can be rectified by proper interventions targeting patients and HCPs.

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AEP494

Vitamin D, osteoprotegerin and metabolic status in children with obesity

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Objective
Determination of changes in metabolic status and vitamin D, osteoprotegerin concentrations in obese children.

Methods
We examined 221 children in the University Hospital (Minsk) from 2017 to 2019 yrs. Their anthropometric parameters (height, weight, body mass index (BMI)) were determined. Blood levels of vitamin D, osteoprotegerin (OPG), insulin were determined. In the biochemical blood test, the parameters of uric acid, glucose were evaluated. All children were divided into 2 groups: group 1 children with morbid obesity – 159 patients (98 boys(B)/61 girls(G)) (BMI more than 99th percentile for sex and age) (BMI 32.95±4.61 kg/m^2, age 14.16±2.28 years); group 2 – 62 patients (B/G=31/31) with alimentary obesity (BMI-95-99th percentile for sex and age) (BMI 27.86±2.04 kg/m^2, age 14.77±2.05 years). The control group consisted of 84 patients (B/G=45/39) with normal body weight (BMI 19.86±2.24 kg/m^2, age 14.32±2.11 years).
Results
In the subgroups of boys with obesity, there were significant differences in the concentration of uric acid in comparison with the control (alimentary obesity 424.10±65.25 mmol/l vs 242.58±49.90 mmol/l (P=0.01)), morbid obesity 324.10±59.33 mmol/l vs 242.58±49.90 mmol/l (P=0.01)). Girls with obesity have a significant increase in uric acid level in comparison with the control group (alimentary obesity 324.10±59.33 mmol/l vs 213.0±39.64 mmol/l (P=0.0001), morbid obesity 409.04±84.23 mmol/l vs 213.0±39.64 mmol/l (P=0.0001)). In boys with obesity higher concentrations of OPG were detected relative to the control group (alimentary obesity 259.98±108.07 ng/ml vs 225.12±55.88 ng/ml (P=0.09), morbid 322.22±82.14 ng/ml vs 225.12±55.88 ng/ml (P=0.001)). In girls with obesity higher concentrations of OPG were detected relative to the control group (alimentary obesity 326.84±104.02 ng/ml vs 254.39±78.29 ng/ml (P=0.046), morbid 347.33±93.50 ng/ml vs 254.39±78.29 ng/ml (P=0.03)). In the obese boys, the level of vitamin D is significantly lower than in the control group (alimentary obesity 29.56±6.01 ng/ml vs 33.02±4.10 ng/ml (P=0.05), morbid obesity 27.56±5.75 ng/ml vs 33.02±4.10 ng/ml (P=0.05)). Obese girls showed a significant decrease in vitamin D relative to the control group (alimentary obesity 24.21±10.75 ng/ml vs 31.34±7.35 ng/ml (P=0.05), morbid obesity 23.52±4,18 ng/ml vs 31.34±7.35 ng/ml (P=0.04)). In boys with obesity higher concentrations of insulin were detected relative to the control group (alimentary obesity 18.9±12.7 µU/ml vs 9.1±4.2 µU/ml (P=0.0001), morbid 28.71±7.36 µU/ml vs 9.1±4.2 µU/ml (P=0.001)). In girls with obesity (alimentary obesity 20.28±6.25 µU/ml vs 14.10±6.80 µU/ml (P=0.001)) morbid obesity 23.32±9.65 µE/ml vs 14.10±6.80 µU/ml (P=0.001)).
Conclusion
Children with obesity have a significant decrease in the concentration of vitamin D. There is an increase in insulin and OPG rates.

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AEP495

Is body mass indexbefore the fast of the month of ramadan associated with the evolution of lipid parameters in diabetic women?

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Aim
The objective of our study is to describe the evolution of the parameters of the lipid balance after fasting in a population of diabetic women, and to determine if the BMI before the fast is associated with the variation of these parameters.
Materials and methods
This is a prospective evaluative study conducted on 44 female patients with type 2 diabetes who have received prior education and therapeutic adjustment adapted according to the recommendations of the ADA 2016.
Results
The mean age was 53.31±11.93 years. The average BMI was 30.33±5.26 kg/m^2. 73.3% (n=33) were at high and very high risk related to fasting (ADA 2016). The days fasted were successive with an average of 24.75±8.7 days. The majority (73.3%, n=33) had fasted for the entire month. 77.6% (n=35) were obese with an average BMI of 31.78±4.4 kg/m^2. There was no significant difference between patients with normal BMI and those who were obese in terms of average age and average number of fast days. HbA1C decreased from 8.49±1.73% to 8.16±1.89% after fasting (P=0.079). The CT, TG, HDL and LDL were respectively 4.67±0.88, 1.2±0.44, 1.15±0.24 mmol/l and 1.15±0, 31 g/l before fasting, respectively. They increased respectively after fasting to 4.62±0.88 (P=0.613), 1.27±0.4 (P=0.197), 1.16±0.24 mmol/l (P=0.873) and at 1.11±0.3 g/l (P=0.326). Either an average decrease of –0.04±0.62 mmol/l of CT, an average increase of +0.07±0.35 mmol/l of TG, an average increase of +0.005±0.21 mmol/l in HDL and an average decrease of –0.039±0.26 g/l in LDL. In obese, the mean change in CT was –0.15±0.57, mmol (+036±0.68 mmol/l in the case of normal BMI, P=0.025). The TG was +0.04±0.37 mmol/l (+0.17±0.29 mmol/l (normal BMI), P=0.349). The HDL values were –0.004±0.2 mmol/l (+0.04±0.25 mmol/l (normal BMI), P=0.57). And that of LDL was –0.07±0.25 g/l (+0.07±0.27 g/l (normal BMI), P=0.139). Thus, BMI was associated only with the variation in CT in our population.
Conclusion
The literature reports disparate results in terms of variation in lipid parameters after the fast of the month of Ramadan. They remain highly sensitive to several factors including diet. Studies on a larger scale are essential to better characterize these variations.

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AEP496

Interrelationship between fasting evaluation of insulin sensitivity, body composition, physical activity and total energy expenditure in obese males

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The prevalence of obesity markedly increased in the last 2 decades. This have asserted researchers' attention to the role of adipose tissue throughout the pathophysiology process of a number of diseases. Fatness, namely abdominal fat, is a risk for insulin resistance, type 2 diabetes mellitus (T2DM), and cardiovascular disease. Physical activity is recommended as one of treatment options for individuals with T2DM. This study aimed to determine the relationship between insulin sensitivity measured by HOMA-IR/QUICKI and: total body fat [measured by dual energy X-ray absorptiometry (DXA)], waist circumference, daily physical activity behavior [measured by the ActiGraph accelerometer]; daily total energy expenditure (TEE) and activity energy expenditure (AEE) [measured by doubly labelled water (DLW)]. Following the collection of fasting baseline blood samples and anthropometric evaluation, 43 obese men (39.38±8.44 years of age) were advised to remain sedentary and not initiating any exercise programme during a period of four weeks of weight-stable diet (an energy balance diet were prescribed for all participants). The participants of this study were part of weight stabilization period from a big weight loss intervention study [Queensland University of Technology (QUT) in Brisbane, Australia]. During this 4-week period measurements of AEE, resting metabolic rate (RMR) and physical activity levels (PALs) were recorded at week-4 and baseline. Participants were instructed to wear the accelerometer GT1 Min the first visit (week-4) and TEE was tracked over a period of time of 14 days. This study showed that obesity (BMIs ranging from 30 to 45 kg/m² and body fat with mean of 39.2±5.3%) is a good predictor of insulin resistance (HOMA-IR=4.69±2.63 and QUICKI=0.31±0.02). The participants had markedly increased cardiovascular risk, with a mean waist circumference of 110.1±8.3 cm. Physical activity was positive correlated at moderate intensity (min/day) with fasting plasma glucose (r=.397, P<.006). The linear regression showed that moderate-intensity physical activity behaviour explained 15% of variation of fasting plasma glucose. The limitations of this study are the capability of GT1M to only capture activities on a flat surface. Another limitation of this study is the inability of energy expenditure measurements from the DLW method to capture aspects of activity such as mode or intensity, which may be more important for stimulating the physiological training adaptations. In conclusion, daily physical activity seems to be a bigger determinant of insulin sensitivity than total daily expenditure.

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AEP497

The effectiveness of complex treatment of obesity on theknee osteoarthritisand the dynamics of cytokines, depending on the degree of weight loss

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Objective
Assess the effectiveness of complex treatment of obesity with the use of orlistat (intestinal lipase inhibitor) on the knee OA (KOA) and the dynamics of cytokines (CRP, IL-6, TNF-α) depending on the degree of weight loss.
Methods
50 female patients (45–65 y.o.) with Kellgren-Lawrence stage II-III KOA and obesity (BMI > 30 kg/m²). Patients in Group 1 ($n=25$) took 120 mg of orlistat 3 times a day in combination with a low-calorie diet and exercise for 6 months. Patients in Group 2 ($n=25$) were recommended non-drug therapy for obesity for 6 months. At baseline and after 6 months, the clinical parameters of the KOA (WOMAC) were evaluated, the quality of life was assessed (EQ-5D). A laboratory study of peripheral blood was conducted at baseline and after 6 months: CRP, IL-6, TNF-α.
Results
After 6 months of complex treatment of obesity with the use of orlistat, patients in Group 1 achieved a significant weight loss of 10.07% ($P<0.05$). Depending on the degree of weight loss in Group 1, 15 patients lost > 10% and 10 patients lost 5–9.9% of the initial body weight. In the 2nd group, an insignificant weight loss of 0.84% ($P>0.05$) was achieved, all patients in Group 2 lost less than 5%. Depending on the degree of weight loss, it is noted that in patients with weight loss more than 5% better than WOMAC (pain, stiffness, functional state) ($P<0.05$), EQ-5D ($P<0.05$) compared with less weight loss. In patients with weight loss > 10%, a significant decrease in CRP level was observed ($P=0.03$) compared with baseline and patients with a 5–9.9% weight loss ($P=0.03$) and < 5% ($P=0.02$). Data for statistically significant changes from TNF-α and IL-6, depending on the degree of weight loss was not detected.
Conclusion
The results of the study demonstrated a significant effectiveness of the complex treatment of obesity in patients with KOA. A decrease in body mass of more than 5% helps to improve the clinical manifestations of KOA. A decrease in body weight of more than 10% demonstrates a decrease in the level of CRP, which suggests an effect on meta-inflammation in OA.

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AEP498

Evolution of comorbidities associated with obesity one year after bariatric surgery, our hospital experience

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Bariatric surgery (BS) improves quality of life and health due to the beneficial effect on the metabolism at multiple levels. Specifically, its effectiveness in weight loss and the attenuation or resolution of comorbidities associated with obesity, means lower morbidity and mortality compared to other types of interventions. The objective is to analyze the evolution of obesity-related diseases after twelve months of follow-up.
Methods
Retrospective study with 31 patients who underwent gastric bypass surgery between May 2017 and January 2019 at the Complejo Hospitalario de Navarra. The statistical analysis was carried out by performing Wilcoxon test and linear regression with SPSS.
Results
Average age of patient is 54 years (s.d. 7.9), 45% (14) of them were men and 55% (17) women. The most frequent comorbidities before BS were: arterial hypertension (68%), obstructive sleep apnea (39%), hypercholesterolemia (32%), diabetes (29%), pre-diabetes (29%), microangiopathy (13%), nonalcoholic fatty liver disease (10%), coronary heart disease (2.5%). Pre-surgical BMI was 43.4 kg/m² (s.d. 4.8), dropping to 30 kg/m² (s.d. 2.8) one year after surgery ($P<0,05$). Percentage of fat-free mass at the begining, measured by TANITA was 54% (s.d. 6.7), increasing by 21,7% to 66,1% (s.d. 8.6) at 12 months ($P<0,05$). The Percentage of Excess BMI Loss (PEBMIL) was 73.65% (s.d. 14.2). Weight loss and decrease in the percentage of fat mass is the basis of the improvement of cardiovascular risk factors. The reduction in prescription of the number of lipid lowering treatments was not significant. However, the lipid profile was significantly improved ($P<0.05$). LDL decreased from 112 mg/dl (s.d. 35) to 96 mg/dl (s.d. 31), HDL from 43 mg/dl (s.d. 10) to 52 mg/dl (s.d. 12), and triglycerides from 154 mg/dl (s.d. 61) to 86 mg/dl (s.d. 39). The percentage of hypertensive patients was reduced by 19%, and the average number of drugs prescribed was also reduced from 2 to 1.8 ($P>0,05$). Complete remission rate of diabetes was 77% (7), with an average Hb1Ac of 6% and a mean basal glucose of 97 mg/dl. As side effects, 79% had some nutritional deficit, with vitamin D being the most frequently supplemented.
Conclusions
In the study population, BS reaches the quality indicators and objectives of recommendations. Weight and fat reduction was the basis for improving metabolic comorbidities and cardiovascular risk factors associated with obesity.

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AEP499

Obesogens and obesity pandemic

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Introduction
Obesity is a worldwide pandemic associated with increased morbidity/mortality and high cost for the society. The prevalence of obesity has doubled in more than 70 countries (including developing countries) since 1980. The number of adult subjects with obesity is around 700 million worldwide. The current pandemic in obesity cannot be explained solely by alterations in food intake and/or decrease in exercise. Obesity pandemic coincides with the marked increase of the industrial chemicals in the environment over the past 60 years.
Obesogens
Humans are constantly exposed to a variety of endocrine disrupting chemicals through air, water, and food. Several categories of chemicals are involved (industrial, agricultural, residential, and pharmaceutical). Some endocrine disrupting chemicals have short half-lives (minutes or hours) while others, highly lipophilic (accumulating in the adipose tissue), have long half-lives (years). Several endocrine disruptors can alter regulation of energy balance and weight control to favor weight gain and obesity. The exposed subjects are predisposed to weight gain despite normal diet and exercise. These endocrine disruptors are called obesogens. The list of obesogenic chemicals is continuously growing. Obesogens promote obesity by inducing an increase in the number of adipocytes and storage of fat. The metabolic programming of obesity risk may be linked to *in utero* or lifetime exposure to obesogens. Exposure to obesogens during development can play a role in the development of obesity later in life (developmental origins of adult disease). The developing fetus and neonate are very sensitive to perturbation by obesogens. In many cases, the damage is irreversible due to lack of protective mechanisms such as DNA repair, competent immune system, or mature blood/brain barrier.
Conclusion
The prevalence of obesity is increasing continuously. Diet and physical activity are not the only contributing factors. The developmental exposures to obesogens play a role in the obesity pandemic. Obesogens alter metabolic processes and predispose some subjects to weight gain and obesity. Urgent interventions, particularly among children, are needed. Exposure to obesogens should be reduced or avoided especially in fetus and neonate.

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AEP500

Comparative effectiveness of three methods for body composition assessment in the verification of manifestations of sarcopenia in obese patients

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Aim of the study was to compare the effectiveness of three methods of body composition assessment such as bioimpedans analysis (BIA), air-replacement bodyplatismography (BodPod) and Dual X-ray absorptiometry Total body program (DXA Total Body) in the verification of reducing of skeletal muscle mass as sign of sarcopenic obesity in obese patients.
Material and methods
The study group included 95 patients aged 21–69 y.o. (average age 53.9 ± 11.05 years) with BMI ≥ 30.0 kg/m². The control group included 37 patients aged 37–69 y.o (average age 50.73 ± 10.6 years) of the same age without obesity with BMI 20.0–29.9 kg/m². Body composition was tested using BIA, BodPod and DXA with calculating fat, lean and skeletal muscles mass (kg) and % in all the patients.

Results
According to BIA the groups differ only in fat mass (FM) 42.75 (4.8;6.3) vs 33.15 (28.4;35.5) kg; $P=0.036$ and did not differ ($P>0.05$) in lean (LM), skeletal muscle mass (SMM) and in % of FM and SMM. According to BodPod analyses groups differed in the FM 3.4 [36.81; 69.94] vs 31.02 [23.22; 38] kg, $P=0.007$, % FM 45.4 [42.1; 53.8] vs 37.7 [28.6; 41.1], $P=0.003$ and % LM – 54.6 [46.2; 57.9] vs 62.3 [58.9; 71.4], $P=0.003$, but had statistically equivalent values of LM 55 [49.48; 67.77] vs 40.36 [33.12; 49.06] kg, $P=0.19$. According to DXA Total Body analyses statistically significant differences ($P<0.05$) have been identified between the groups in FM and % FM of the hands, feet, trunk, total body ($P>0.05$), but not in LM and % LM ($P>0.05$).
Conclusions
From methods of body composition assessment, air-replacement bodyplatismography (BodPod) is the most sensitive in the verification of skeletal muscle mass reduction in obese patients. This method shows that patients with obesity have a significantly reduced muscle mass compared with normal weight or overweight subjects.

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AEP501

Combination of topiramate and empagliflozin is considered a good option for treatment of obesity

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Objectives
The aim was to show if the combination of topiramate and empagliflozin have the greatest weight decreasing effect in comparison to each drug alone and to control.
Design
Observational cohort prospective study 6-month trial.
Materials and methods
Observational cohort prospective study with the following of 200 obese patients who were in 4 parallel groups. Had been monitored in a private clinic, each group 50 patient's number, with 35 females and 15 males with 50 patients as a control.
The results show that both topiramate and empagliflozin have weight loss effect if used alone with significant *P*-value which is 0.0480 with topiramate and 0.0048 with empagliflozin and the greatest weight loss effect if used in combination with a *P*-value less than 0.0001.
Conclusion
Combination of topiramate and empagliflozin show a considerable reduction of body weight and so is considered as an option for treatment of obesity.
Keywords: obesity, empagliflozine, topiramate, combination therapy.

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AEP502

Different short-term responses of image dissatisfaction and distortion to sleeve gastrectomy

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Introduction
Bariatric surgery is one of the most important treatment modalities for obesity. Studies suggested that obese subjects have distorted body image perception. Dissatisfaction with body shape is one of the leading reasons for treatment referral.
Aim
To prospectively study body image perception and its relationship with body composition in patients treated with bariatric surgery.
Methods
Nineteen patients were evaluated before and after sleeve gastrectomy using the Stunkard Figure Rating Scale (SFRS) and bioimpedance. Image dissatisfaction and distortion, body mass index (BMI), body fat percentage, muscle mass, and visceral fat were studied.
Results
Fifteen women and four men (mean age = 41.63 ± 10.17 years) were investigated. After surgery (3.7 ± 1.4 months), BMI decreased from 42.53 ± 6.53 to 33.88 ± 5.55 kg/m^2 ($P=0.0001$), body fat from 49.21 ± 4.33 to 43.21 ± 4.76% ($P=0.003$), visceral fat index from 23.3 ± 2.6 to 17.6 ± 4.9 ($P<0.0001$), and muscle mass from 32.13 ± 6.29 to 28.75 ± 6.67 kg ($P=0.0002$). According to the SFRS, all subjects presented image dissatisfaction both at baseline and after surgery. However, dissatisfaction scores were higher at baseline (4.2 ± 1.4) than postoperatively (2.9 ± 1.3, $P=0.0008$). Dissatisfaction was correlated with BMI ($r=0.4632$, $P=0.0034$), body fat percentage ($r=0.5284$, $P=0.0006$), and visceral fat index ($r=0.4457$, $P=0.0050$). In the multiple regression model, after the adjustment for the influence of other variables, body fat percentage was identified as the main influence on the dissatisfaction scores. When self-image distortion was present (pre- and postoperative prevalence of 45.8 and 54.2%, respectively), it consisted of underestimation of body shape and scores did not change significantly after surgery (0.68 ± 0.67 vs 0.89 ± 0.74, $P\pm0.2590$). Women had a higher relative risk of image distortion than men ($RR=1.522$, $P=0.0391$).
Conclusion
All patients presented image dissatisfaction both preoperatively and after a short postoperative period. Dissatisfaction improved significantly after sleeve gastrectomy as a result of a decrease in body fat percentage. Nevertheless, there was no significant change in image distortion, a common feature in this cohort and reportedly involved in the very pathogenesis of obesity.

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AEP503

Impact of isoflavone intervention on microbiota, predicted metagenome and metabolic profile in polycystic ovary syndrome

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Objective
Polycystic ovary syndrome (PCOS) affects 5–20% of women of reproductive age worldwide and is associated with disorders of glucose metabolism. Hormone and metabolic signalling may be influenced by phytoestrogens, such as isoflavones. Their endocrine effects may modify symptom penetrance in PCOS.
We investigated, whether women with PCOS and healthy controls differ in their capacity to metabolize dietary isoflavones and whether this capacity is associated with PCOS-typical metabolic, microbiome and predicted metagenomic markers.
Objectives
After clinical and biochemical characterisation, urine isoflavone levels were measured in PCOS and control women before and 3 days after a defined isoflavone intervention via soy milk. In parallel, bacterial equol production was evaluated using the log (equol:daidzein ratio) and microbiome, metabolic and predicted metagenome analyses were performed. Urine isoflavone and equol levels were measured by mass spectrometry in women with PCOS ($n=24$) and non-PCOS controls ($n=20$) before and after 3 days ofsoy challenge. Bacterial equol production was evaluated using the log(equol:daidzein ratio). Group size was calculated according to the effects of equol. Metagenome analyses were performed using PiCRUST (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States), LEfSe (Linear discriminant analysis effect size) and QIIME1.9 (Quantitative Insights Into Microbial Ecology).
Results
We found metabolic changes, decreased glucose ($P=0.01$) and fasting insulin ($P<0.01$) as well as a decreasedrespective HOMA2-IR ($P<0.02$) in PCOS patients, but not in control women ($P=0.48$, $P=0.70$, $P=0.72$) after isoflavone intervention. Investigating the effect of an equol rise on androgenic as well as fertility markers, these two categories correlated negatively with the rise of equol (-0.364, $P=0.021$, -0.396, $P=0.021$ resp.). In addition, we found PCOS-associated predicted metagenomic pathways improved after soy intervention with specific strains linked to carbohydrate metabolism as well as inflammation being increased in PCOS women but not in controls.
Summary and conclusions
There is increasing evidence on specific interactions between energy metabolism, hormone systems and bacterial pathways e.g. via active intestinal

compounds. The importance of the equol producing gut microbiota and metagenomic pathway changes in PCOS women may therefore be considered from a new perspective. However, dietetic and microbiota-associated aspects in PCOS should be investigated in more detail in the near future.

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AEP504

Genetic variability in antioxodative and inflammatory pathways modifies the risk for PCOS and influences metabolic profile of the syndrome

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Background
Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder of multifactorial etiopathology likely to involve the interactions between genetics and lifestyle. Chronic inflammation and oxidative stress (OS) may participate in the pathophysiology of the syndrome. The question of the extent to which OS and inflammation are causally related to the development of the syndrome and metabolic complications remains unanswered. Furthermore, the role of NLRP3 inflammasome as an important trigger of inflammatory pathways and *NLRP3* and *CARD8* polymorphisms have never been addressed in PCOS yet.
Purpose
The aim of our study was to investigate genetic variability in the pathways associated with OS and inflammation and to assess their relationship with the risk of PCOS development as well as with metabolic characteristics in PCOS patients.
Methods
We conducted a case-control study conducting of total 169 Slovenian PCOS patients and 83 healthy blood donors. They were genotyped for polymorphisms in antioxidative (SOD2 rs4880, CAT rs10 01179, PON1 rs85 4560, and rs662) and inflammatory pathways genes (NLRP3 rs35 829419, CARD8 rs20 43211, *TNF*α rs18 00629, *IL1*β rs11 43623, and rs16 944, IL6 rs18 00795) using competitive allele-specific polymerase chain reaction (PCR). Logistic regression and Mann-Whitney test were used in the statistical analysis.
Results
SOD2 rs4880, CARD8 rs20 43211 and *IL1* rs16944 were associated with the risk of developing PCOS. Furthermore, the interactions between CARD8 rs20 43211 and *IL6* rs18 00795 and between *IL1*b rs11 43623 and IL6 rs18 00795 also significantly affected the risk for PCOS. With regards to glucose homeostasis, *CAT* rs10 01179, SOD2 rs4880, PON1 rs85 4560, *NLRP3* rs35 829419, and *TNF*α rs18 00629 were significantly associated with response to the glycaemic load.
Conclusions
Our data indicates that genetic variability in antioxidative and inflammatory pathways influences the development of PCOS and glucose homeostasis in PCOS patients.

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AEP505

Challenging hypoglycaemia management in a patient with metastatic insulinoma

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Background
Metastatic insulinomas are very rare (fewer than 1:100000) and therefore may pose a therapeutic challenge as there are no case controlled studies comparing the efficacy of various therapeutic approaches avialable. The Ki 67 index from the histology of the primary tumour is an established prognostic marker for metastatic disease with tumours showing low Ki 67(<3%) being defined as low risk of early recurrence.
Case Presentation
A 60 year old female presented with severe episodes of fasting hypoglycaemia with glucose levels as low as1 mmol/l requiring prolonged dextrose 10% infusion. This was accompanied by raised insulin and C-peptide values when confirmed severe hypoglycaemia occured (>100 mU/l and 2953 pmol/l, respectively). Her past medical history included a distal pancreatectomy and splenectomy fourteen years ago when she had an incidental finding of a cystic lesion in the pancreas. The histology at the time revealedit was a low grade pancreatic neuroendocrine tumour (NET). For the next 5 years she was having regular follow ups with repeat imaging of her abdomen and repeat chromogranin A and B levels and as there was no evidence of tumour recurrence hence she was discharged from the surgical follow up. Repeat CT imaging revealed multiple large volume liver metastases (largest measuring 11.3 cm), an 8.2 cm left para-aortic metastatic tumour deposit anda smaller metastatic deposit anterior to the left renal vein. CT guided biopsy showed a grade 2 well differentiated NET with Ki 67 4.5%. Despite commencementand uptitration of diazoxide (100 mg TDS) and octreotide (200 mg TDS), patient continued to have symptomatic severe hypoglycaemic episodes requiring continous 10% dextrose infusion at 125 mls/hour. She also developed drug-induced rash. Following a multidisciplinary team discussion, decision wasmade to perform hepatic artery embolisation but despite that the hypoglycaemic episodes recurred the next day. Eventually, patient under went laparatomy for right hemihepatectomy and resection of the left retroperitoneal mass. She was euglycaemic after the procedure and had a good postoperative recovery. Subsequent histology showed well differentiated grade 2 NETconsistent with metastatic spread of previous pancreatic neuroendocrine tumour (insulinoma). She remains euglycaemic and well.
Discussion
This case illustrated that metastases from a neuroendocrine tumour may occur many years since initial presentation. Metastatic insulinoma may be quite challenging to manage. The initial approach is to manage symptoms pharmacologically whilst decision is made regarding definite management with options including surgery, embolization, radiotherapy, chemotherapy or liver transplant depending on individual circumstances.

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AEP506

Does the pilgrimage increase the podiatry risk in diabetic patients?

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Background
The number of diabetic pilgrims could exceed 220000/year. Among the complications that can be observed in these patients, foot lesions are very common. We are therefore interested in this study in the assessment of podiatric risk among diabetic pilgrims.
Material and methods
A Cross-sectional study covered 43 diabetic patients from the city of Sousse, intending to perform the pilgrimage during 2019. The evaluation was made before and after pilgrimage and included clinical examination, evaluation of neuropathy and peripheral arterial disease.
Results
The average age of patients was 62.5±5.4 years. Diabetes was in chronic imbalance in 39.5% of cases with an average glycated hemoglobin of 7.9±1.3%. The clinical exam after the return of pilgrimage showed that the most frequent pological lesions were hyperkertosis (96.8%) as well as superficial fungal infections. Three patients had food ulcers which were mainly due to walking injuries and unsuitable shoes. The study of the risk of developing a foot ulcer showed that it was significantly associated with a lower total cholesterol, HDL cholesterol or LDL cholesterol and a higher triglyceride level (*P* respectively 0.02; 0.02; 0.01 and 0.04). The study of the other risk factors had not shown any significant correlation. However, there was a significant increase in the systolic pressure index in the left as well as the right foot after the pilgrimage (1.03±0.19 vs 1.11±0.19 and 1.03±0.28 vs 1.11±0.18, $P<0.05$)
Conclusion
The Pilgrimage increases the risk of developing foot injuries among diabetic patients. Therefore, an assessment and an adapted care to the grade of risk are essential before, during and after the pilgrimage.

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AEP507

Diabetic foot: An important, yet underestimated complication in albanian healthcare

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Diabetic foot is a main complication of Diabetes Mellitus that affects 15–25% of diabetes patients at least once in their lifetime. This complication has severe consequences at patient's life quality and a high cost not only for the patient but also for the society. However, this complication is still underestimated in Albania.
Aim of study
Our main objective is to summarize the causes and pathogenic mechanisms leading to diabetic foot, and to focus on the management of this important health issue.
Materials and method
This is a prospective study with homogenous cohort. All DF patients presented at our clinic from April 2016 to December 2018.The patients were evaluated for the risk factors like neuropathy, peripheral arterial disease and also the different elements of diabetic foot management. There were studied 131 patients. The data was analysed according to IBM SPSS Statistics 23.
Results
Out of 131 patients enrolled (124 of them had Diabetes mellitus tip II, 7 had Diabetes mellitus tip I), aged from 41 to 91 with a mean age of 63.5. Mean diabetes duration was 12.3 years. 85% of the wounds were infected. We isolated a total of 32 strains. Among them 10 were the most alert pathogens identified (*Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Enterococcus faecalis, Staphylococcus spp, Proteus vulgaris, Proteus mirabilis*, *Streptococcus b-haemoliticus, Klebsiella pneumoniae, Acinobacter baumanii*). The most sensitive antibiotic was Ceftriaxone and the most resistant was Ciprofloxacin. According the local surgical treatment minor amputations were present in 69 patients, debridement in 47 patients. Negative pressure wound therapy was used in 23 patients.
Conclusion
A multidisciplinary approach should be employed because of the multifaceted nature of foot ulcers and the numerous comorbidities that can occur in these patients.

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AEP508

Diabet foot unit of the marqués de valdecilla university hospital: A data-analytic look of a multidisciplinary team

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Objective
We will analyze various characteristics of the patients who attend the HUMV Diabetic Foot Unit for a week. The variables studied are sex, age, type of diabetes, years of evolution, type of current treatment, last glycosylated hemoglobin, presence of other cardiovascular risk factors and existence of previous ulcerations and amputations
Material and methods
We worked with Microsoft Excel to coollect the data and perform the statistical study.
Results
We analyze 64 patients, with a mean age of 69.78±3.13 years with the following distribution by sex: 57.81% of men and 42,19% of women. Regarding the type of diabetes, we found 89.06% of type 2 diabetes and 10.94% of type 1 diabetes. We observed an average of 16.45±1.73 years of diabetes evolution with a last HbA1c mean of 7.73±0.36%. The treatment followed included insulin therapy in 70.31% of patients compared to an exclusively oral treatment in 29.69%. About the existence of other cardiovascular risk factors: arterial hypertension was present in 87.50%, dyslipidemia in 76.56% and patientes who had the three cardiovascular risk factors reached 70.31%. Regarding smoking, 14,06% of the patients declared active consumption, 34.38% reported being former smokers and 51.56% denied their use. There are other predisposing factors of diabetic foot, 35% of patients were diagnosed with peripheral arterial disease and 21.67% with diabetic neuropathy; both pathologies were in 10% of patients and only 33.33% had none of them. Focusing on the pathological history of history of his lower extremities, 62.50% had presented previous ulcerations, while for 37.50% of the patients it was their first diabetic ulcer. The incidence of amputations reached 34.38% representing 55% in patients with a previous history of ulcerations. Regarding the origin of the patients, 40.35% had been referred from Endocrinology and Nutrition Department, 21.05% from Primary Care, 8% from Cardiocascular Surgery Department and the remaining 14.04% came from other specialties.
Conclusions
We verify that patients treated in this unit have a very high cardiovascular risk, so it would be necessary to consolidate multidisciplinary teams of diabetic foot to work on the prevention of risk factors and treat concomitant pathologies that avoid the high number of amputations with important human, social, and economic consequences.

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AEP509

Lower urinary tract symptoms in patients with metabolic syndrome and life quality impact: Preliminary results

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Introduction
Recent epidemiological surveys have demonstrated a significant association between MS and lower urinary tract symptoms (LUTS). The aims of this study were to determine LUTS in patients with metabolic syndrome (MS) and to evaluate their impacts in patients' life quality.
Patients and methods
A cross-sectional study was conducted on patients with metabolic syndrome MS diagnosed according to the criteria of the US National Cholesterol Education Programme Adult Treatment PanelIII (NCEP ATP III). Clinical evaluation included body mass index (BMI) and waist circumference measurement. Biological data were also collected including fasting blood sugar, postprandial glycemia, glycosylated hemoglobin (HbA1c), cholesterol and triglyceride levels. Lower urinary tract symptoms were assessed using the urinary symptom profile (USP) questionnaire and the impact in life quality was evaluated using Ditrovie score.
Results
Forty patients were collected with a mean age of 60.2 years (±10.5) and a sex-ratio of 0.5. All patients were diabetic and 62.5% had hypertension. The mean BMI was 26.6±5.8 and waist circumference was 98.8±8.3 cm. Mean USP total score was 11.1±7.8. Overactive bladder symptoms were found in 60% of the patients, stress incontinence symptoms in 50% of the cases and dysuria in 22.5% of them. Mean Ditrovie score was 2.25. The USP total score wasn't correlated to age ($P=0.07$) nor to fasting blood sugar level ($P=0.89$) nor to HbA1C level ($P=0.29$). Ditrovie score was significantly correlated to the overactive bladder USP score ($P=0.014$).
Conclusion
LUTS are frequent in patients with MS including meanly Overactive bladder symptoms and stress incontinence symptoms. Their impact in life quality is correlated to overactive bladder symptoms.

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AEP510

Fungal necrotizing otitis externa in diabetic patients: Clinical features and diagnostic difficulties

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Objectives
To describe and analysis theimpact of diabetes on clinical presentation andthe difficulties we could affront within the management of this entity.

Materials and methods
A retrospective study conducted between 2006 and 2019 based on 24 patients managed at our Otolaryngology Head and Neck Surgery Department.
Results
24 poorly controlled diabetic patients were enrolled in this study: 15 men and 9 women, with a mean age of 66 years. All patientspresented severe and persistent otalgia and otorrhea. External auditory canal narrowed:19 cases, granulation tissue 7 cases, polyp in 5 cases; facial nerve pulsy: 5 cases. Destruction of the bony meatus (79%), mastoid 25%; the obliteration of normal soft-tissue planes at the skull base 12,5%, the parapharyngeal extension 4% and the temporomandibular joint (4%) were documented by CT scans. Diagnosis was reviewed after a lack of response to antibiotic therapy it was established based on the Ear swabs for culture andhistopathologic. Aspergillus flavus (41%) and Candida (47%) were the fungal agents isolated. 2 patients were treated without identifying the causal fungus. Voriconazole was the first-line therapy, with a median length of treatment of 2 months. 2 patients underwent a mastoidectomy. The clinical outcome was favorable with 18 patients free of disease whose diabetes was controlled, otological sequelae were reported. 4 patients were not followed up.
Conclusion
It is a serious disease with high morbidity-mortality rate especially for poorly controlled diabetic patients. Underestimation of the entity may lead to a prolonged and ineffective treatment.

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AEP511

HNF1A MODY revealed by recurrent hypoglycemia

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Introduction
Hepatocyte nuclear factor 1A MODY (HNF1A-MODY) is the most common form of Maturity-onset diabetes of the young (MODY) diagnosed in adults. It is caused by heterozygous mutations in the *HNF1A* gene and is associated with progressive β-cell failure and increasing hyperglycemia due to reduced insulin secretion. HNF1A-MODY is characterized by a large phenotypic variability. We herein report the case of a 40-year-old diabetic woman who was identified as having mutation of the HNF1A gene, after repeated hypoglycemia under insulin therapy.
Case report
A 40-year-old woman was admitted to our diabetology department for the management ofuncontrolled diabetes due to an abrupt withdrawal of insulin therapy. She had a family history of diabetes on oral antidiabetics in her mother and her two paternal aunts. Her diabetes was discovered at the age of 24 year old by an asymptomatic glycosuria. She was put at the age of 27 year-old, during her first pregnancy, under insulin therapy. After delivery, the patient reported recurrent hypoglycemia and an important weight gain despite lowering the dose of insulin. She had extremely poor glycemic control secondary to non-compliance with insulin and her glycated hemoglobin (HbA1c) ranged between 9% and 11.5%. Assays of antiglutamic acid decarboxylase (anti-GAD) and anti-islet antigen 2 (anti-IA2) antibodies were performed during hospitalization and were negative. A C-peptide testing, concomitant with normal glucose level, was normal (0.8 ng/ml). The molecular study identified a novel truncating mutation in the HNF1A gene (*P*.Gly292fs). The patient treated by a low dose of sulfonylureas (Gliclazide 30 mg) and an Inhibitors of dipeptidyl peptidase 4 (sitaglipitin 100 mg) with a good glycemic control and the absence of recurrent hypoglycemia.
Conclusion
Our case showed the interest of evoking the diagnosis of HNF1A diabetes in the presence of recurrent hypoglycemia under low dose of insulin in a diabetic person.

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AEP512

Development of diabetic complications in patients with type 2 diabetes mellitus and impaired circadian rhythms

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The study involved 37 people with type 2 diabetes who received oral hypoglycemic medications, aged 35–65 years. The first group included 22 people with a daily work schedule, and the second group included 15 people with a night work schedule of more than 5 years as a model of patients with impaired circadian rhythm. Comparative analysis of descriptive data shows the predominance of creatinine levels ($P<0.05$) and, accordingly, a decrease in GFR (P 0.05) in the group of patients with night mode. Despite poor glycemic control, long duration of DM2, AH, and greater age in the group of patients working during the day ($P<0.05$), GFR values in both groups do not differ statistically, which indicates a decrease in the filtration capacity of the kidneys in both groups. The earlier decrease in the filtration capacity of the kidneys in group 2 can be explained by a higher level of glycemic variability, the value of which has a direct correlation with the level of creatinine ($r=0.656$; $P<0.05$) and the reverse – with GFR ($r=–0.657$; $P<0.05$). Despite the significant difference between patients 'age, diabetes experience, and carbohydrate metabolism, there was no statistically significant difference between TSS and NIS-LL in the groups. Correlation analysis showed that the severity of diabetic polyneuropathy in group 1 patients was negatively affected by weight gain, AH experience (TSS scores positively correlated with BMI ($r=0.564$; $P<0.05$) and AH experience ($r=0.472$; $P<0.05$)) and SD2 experience (NIS-LL has a positive correlation with SD2 experience ($r=0.459$; $P<0.05$) and AH experience ($r=0.312$; $P<0.05$)), and an increase in HDL leads to an improvement in the course of diabetic polyneuropathy. indicators of polyneuropathy (TSS and NIS-ll) are negatively correlated with the level of HDL ($R=–0.4$; $P<0.05$).Similar data were obtained in other studies. In group 2 patients, the severity of diabetic polyneuropathy, according to TSS scales, is negatively affected by an increase in LDL ($r=0.550$; $P<0.05$), cholesterol ($r=0.516$; $P<0.05$), and glycemic variability ($r=0.330$; $P<0.05$). The manifestation of diabetic polyneuropathy in group 2 of the same degree as in group 1 patients can be explained by the higher variability of glycemia in patients with night mode.

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AEP513

Anemia is associated risk factor of chronic kidney disease in diabetes type 2 patients

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Introduction
Diabetes is the leading cause of chronic kidney disease (CKD) and is associated with excessive cardiovascular morbidity and mortality. On the other hand, anemia is common among those with diabetes and CKD and greatly contributes to patient outcomes.
Aim
The aim of this study was to investigate the prevalence and associated risk factors of CKD among the patients with diabetes type 2 (DT2).
Methods
We examined at baseline 300 patients with DT2 and CKD aged between 30 and 65 years. Control group included 100 patients without diabetes the same age. Blood samples for measurement of routine chemistry were taken after an overnight fast of at least 12 hours. The albumin and creatinine levels were measured for albuminuria and estimated glomerular filtration rate (eGFR) assessment. Anemia was defined as hemoglobin level <13 g/dl in men and <12 g/dl in women. Univariate and multivariate logistic regression analyses were conducted to identify factors associated with CKD.
Results
The total prevalence of anemia was higher in patients with DT2 in comparison to control (57.3% vs 28.6%, $P=0.003$). Prevalence was higher in diabetics with decreasing eGFR (P for trend 0.001). In multivariate analyses, anemia (OR = 8.167, 95% CI : 3.785–35.145), hyperuricemia (OR = 0.956, 95% CI : 0.918–0.975) and hyperhomocysteinemia ($R=1.856$, 95% CI : 1.718–1.975) were independently associated with the presence of CKD.
Conclusion
Prevalence of anemia progressively increases with advancing stages of CKD and is higher in patients with DT2 than matched non-diabetic patients. Thus, common chronic non-communicable diseases, including diabetes, anemia, hyperhomocysteinemia, hyperuricemia were associated with greater prevalence of CKD.

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AEP514

Lipid metabolism in patients with diabetic nephropathy

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Introduction
Diabetes is the most common endocrine disease in the world. Persistent hyperlipidemia in type 2 diabetes is accompanied by damage to various organs, on the basis of which generalized changes in the microvasculature lie. In patients with diabetes mellitus with chronic kidney disease, dyslipidemia can be aggravated with hyperglycemia and insulin resistance. Control of dyslipidemia is an important therapeutic goal, since normalization of lipid metabolism and glycemic status reduces the risk of renal complications in type 2 diabetes. Aim of the work to study lipid metabolism in patients with type 2 diabetes mellitus with diabetic nephropathy.
Materials and methods
The study included 50 patients with type 2 diabetes. Group 1 of 25 patients with type 2 diabetes mellitus did not have a history of diabetic nephropathy; Group 2 of 25 patients had chronic kidney disease (CKD-C2, A2) with type 2 diabetes. The median age was 52.7±3.78 years: type 2 diabetes was 8 years: BMI-27.6: Hb1C-10.5%: Fasting glycemia – 8.8 mmol/l.
Results
Dyslipidemia was observed in 37% of type 2 diabetes without CKD and 78% of type 2 diabetes with CKD. Patients with atherogenic VLDL dyslipidemia, a high level of TG+VLDL was 25% among patients with type 2 diabetes and 71% among patients with type 2 diabetes with CKD. GFR in patients with type 2 diabetes was 89 ml/min, patients with type 2 diabetes with GFR 65 ml/min.
Conclusion
According to our results, we can conclude that lipid metabolism is significantly impaired among patients with diabetic nephropathy. Depending on the course of CKD, lipid metabolism is also exacerbated. Regular screening of diabetic nephropathy with dyslipidemia can be useful for controlling the risk of macrovascular complications.

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AEP515

Increased ultra sensitive CRP: Abiomarker of microvascular risk in men with type 2 diabetes

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Introduction
RaisedCRP is observed in obesity, metabolic syndrome and type 2 diabetes in the absence of any inflammatory or infectious disease. Indeed, it may constitute a mark of cardiovascular risk and macro and micro-vascular complications. The objective of our study is to assess the association between raised ultra-sensitive CRP and macro-vascular and micro-vascular complications in a group ofpatients with type 2 diabetes (T2DM).
Materials and Methods
A comparative retrospective observational study including 176 patients with T2DM followed in department C of the NationalNutrition Institute of Tunis. Clinical and biological data were collected from medical records. Patients were classified into two groups according to the level of ultra-sensitive CRP (Group 1: low CRP < 3 mg/l and group 2: high CRP ≥ 3 mg/l).
Results
The mean age was 58.8±12 years. A female predominance was noted (62%). The mean duration of diabetes was 12±7.7 years. The average BMI was 28.9±5.4 kg/m^2. The average HBA1c was 10.5±2.3%. Half of the patients were on insulin (49.2%). The mean CRP was 5.1±4.3 mg/l with no significant difference between the two sexes. Two-thirds of women (71.6%) and 38% of men had high CRP (P=0.02). Patients with elevated CRP were on insulin and had higher BMI and uric acid levels (P=0.008, P=0.037 and P=0.04 respectively). Macro and micro-vascular complications were noted in 23.3% and 52.2%, 38.8% and 57.7%, 13.8% and 53.2%, in the whole population, in male patients and female patients respectively. Depending on gender, there was not a significant difference regarding macrovascular complications (coronary artery disease, stroke and peripheral artery disease) between patients with normal or elevated CRP. In contrast, in men the prevalence of micro-angiopathy, represented by diabetic nephropathy (27%) and diabetic retinopathy (47.5%), was higher in patients with elevated CRP (P=0.02).
Conclusion
Our study found that women with type 2 diabetes had higher CRP levels. In contrast, raised CRP was associated with a higher risk of microvascular complications, mainly diabetic retinopathy and nephropathy, in men with type 2 diabetes.

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AEP516

Evaluation of anxiety frequency in school-aged children with diabetes mellitus type 1 depending on carbohydrate metabolism compensation

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To study anxiety frequency in school-aged children with diabetes mellitus type 1 (DM type 1) depending on carbohydrate metabolism compensation.
Materials and methods
96 patients with DM type 1 aged 13.9±1.97 years. Diabetes duration is 1.72±22.33 Year. We determined glycated hemoglobin (HbA1). The level of HbA1 of 7.5% or more indicated the decompensation of carbohydrate metabolism. Evaluation of the anxiety level was carried out using the Spilberger-Hanin scale of self-assessment of anxiety with the determination of reactive (RA) and personal anxiety (PA). The patients were divided into 2 subgroups: group 1 with HbAl level of 7.5% and higher (n=35) and group 2 with HbAl level under 7.5% (n=61).
Results
In group 1, high PA was detected in 10 people (28.6%), and high RA in 13 people (37.14%). In group 2, high PA was detected in 11 people (18.0%), and high RA in 9 people (14.7%). The incidence of high PA in group 1 was significantly higher than in group 2 (χ^2=5.75, P±0.01). The frequency of RA in group 1 was also higher than in group 2 (χ^2=8.81, P=0.03). The risk of developing high PA significantly increased the growth of HbAl level (b=0.16) (Exp (b)=1.18; 95% CI–1.03±1.34; P<0.02).
Conclusion
The frequency of high anxiety occurrence, both personal and reactive, is significantly higher in patients with decompensation of carbohydrate metabolism. The risk of developing high personal anxiety increases with the progression of decompensation of carbohydrate metabolism.

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AEP517

Prevalence of peripheral and cardiac autonomic neuropathy in hypertensive pre-diabetic georgian patients by Sudoscan

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Background
Sudomotor function is used to assessperipheral autonomic system. Electrochemical Skin Conductancemeasurement using electrochemical reaction betweenchloride ions in sweat and stainless steel plate electrodes is a simple, non-invasive and quick method. Several factors, including age, sex, BMI, glycemic status influence sweat function.
Aim
Our aim was to determineprevalence of peripheral (DPN) and cardiac autonomic neuropathy (CAN) in hypertensive pre-diabetic patients by Sudoscan.
Methods
Based on their glycemia status participants (n=70) were divided into 2 groups (Gr.):Gr.1– n=38, 20 men/18 women (mean age 63.2±4.3 yrs)

had impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) or IFG+IGT and hypertension; Gr. 2–$n=32$, 18 men/14 women (mean age 62.8±3.6 yrs) had hypertension, but no IFG/IGT or IFG+IGT. Following tests/analysis were performed in all thd patients: Sudoscan test, HbA1c, oral glucose tolerance test (OGTT), BMI, LDL-C, TG, systolic and diastolic blood pressure (SBP, DBP). According to Sudoscan results neuropathy is defined as: 1) no neuropathy: >70 (feet)/>60 (hands); 2) moderate neuropathy: 50–70 feet/40–60 hands; 3) severe neuropathy <50 (feet)/<40 (hands). CAN was defined according to CAN risk score: <30–no risk of CAN; ≥30 – at risk of CAN. There was no significant difference in sex, age, SBP/DBP between the groups.
Results
Among Gr.1 patients with pre-diabetes and hypertension prevalence of moderate or severe neuropathy, both DPN and CAN, was more prevalent (no neuropathy – 4 patients/10%; moderate neuropathy – 20 patients/52%; severe neuropathy – 14 patients/36%; CAN–<30–29 patients/76%; ≥30–9 patients/23%), than in Gr. 2 ones without IFG or IGT, or IFG+IGT (no neuropathy – 16 patients/50%, moderate – 12 patients/37.5%, severe-4 patients/12.5%; CAN <30–4 patients/12%; ≥30–28 patients/87%). HbA1c (%) and OGTT were higher in Gr.1, than in Gr.2 patients (5.9±0.3 vs 4.1±0.5, $P=0.005$). There was no statistically significant difference in LDL-C/mmol/l (2.32±0.9 vs2.14±0.4, $P=0.85$) and TG/mmol/l (2.02±1.2 vs 1.9±0.9, $P=0.93$) levels between the groups, while BMI(kg/m^2) was higher in Gr.1 compared to Gr.2 (33.7±2.3 vs 27.2±1.2, $P=0.01$).
Conclusion
The overall prevalence of DPN and CAN was higher in hypertensive patients with pre-diabetes than in those without pre-diabetes. Thus, Sudoscan is an easy, non-invasive and quick method to detect DPN or CAN in an early stage. Though further studies are necessary to approve Sudoscan advantage over other well-known diagnostic methods.

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AEP518

Hyperuricemia as independent cardiovascular risk factors in T2D

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Background
Uric acid is an inflammatory factor and may have a role in endothelial dysfunction and act as a mediator of diabetic nephropathy. Hyperuricemia is a risk factor for cardiovascular events and renal insufficiency in diabetic patients. The aim of this study was to evaluate the relationships between serum uric acid concentration and level of urinary albumin excretion as well as markers of subclinical atherosclerosis in patients with type 2 diabetes mellitus.
Materials and methods
A cross-sectional analytical study was conducted in 120 patients with T2D without a history of gout. Serum uric acid and urinary albumin-creatinine ratio were determined. The relationships between serum uric acid concentration and carotid intima-media thickness or plaque score were investigated additionally in these patients. Other metabolic parameters including lipid profile, hemoglobin A1c, glomerular filtration rate, body mass index, blood pressure, blood glucose.
Results
The mean age of the patients was 58.45±10.11 years old. Serum uric acid levels for normoalbuminuric, microalbuminuric, and macroalbuminuric patients were 4.44±1.17 mg/dl, 4.97±1.68 mg/dl, and 7.27±1.08 mg/dl, respectively. Serum uric acid level correlated positively with urinary albumin-creatinine ratio ($P=0.04$). Positive correlation was found between serum uric acid concentration and intima-media thickness ($r=0.233$, $P=.0087$).There was a significant relationship between hyperuricemia and serum triglyceride, fasting blood glucose, hemoglobin A1c, glomerular filtration rate, and serum creatinine levels ($P<0.001$).
Conclusions
Serum uric acid concentration is associated with microalbuminuria and subclinical atherosclerosis in patients with type 2 diabetes mellitus. So, we conclude that serum uric acid plays a role in diabetic nephropathy as well as in cardiovascular eventsin T2D.
Keywords: diabetes, uric acid, proteinuria, atherosclerosis.

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AEP519

Neurological disorder in a patient with decompensated T2DM

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Introduction/aim
Neurological symptoms are rarely related to decompensated type 2 diabetes mellitus. However, thanks to complementary tests, we can identify this association more easily.
Material and method
Review of the patient's clinical record and the relevant literature.
Results
A 76-year old man complained in the last year of a progressive, involuntary and disabling movement disorder consisting in hemichorea of the left upper and lower limbs. He presented psychotic thoughts, cognitive impairment, as well as moderate weight loss. He had a clinical history for more than 10 years of a poorly controlled type 2 diabetes mellitus (haemoglobin A1c 14.4%) treated only with 20 units of glargine insulin daily, moreover with irregular adherence. No diabetic complications had been described. He also suffered from dyslipidaemia without pharmacological treatment, anxiety and depressive disorder, subclinical hypothyroidism, a lack of self-care, and a smoking habit. His medication included omeprazole 20 mg per day and atenolol 50 mg per day. In the lab test there was nothing remarkable, apart from high glucose levels (around 200–300 mg/dl), and low total plasmatic protein concentration (5.67 g/dl). Tests for HIV and drugs were negative. An MRI of the brain showed high signal intensity of right-basal ganglia on T1-weighted images, in particular on putamen, which could be associated with a case of non-ketotic hyperglycemia-induced hemichorea. Once the right treatment for his diabetes was established (20 UI glargine insulin, plus 12 units in total of insulin aspart daily) and his capillary glucose levels were in range, the choreiform movements gradually improved until they were completely absent.
Conclusions
When considering neurological disorders, we rarely associate those with diabetes mellitus; however, sometimes we must think out of the box to reach the correct diagnosis. Although there haven't been many confirmed cases until now, we should include non-ketotic hyperglycemia in the differential diagnosis of acute movement disorders such as chorea.

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AEP520

Short and long-term glycemic variability associated with severe hypoglycemia and retinopathy in type 1 diabetes mellitus

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Introduction
Severe hypoglycemia and retinopathy are two of the main complications of diabetes mellitus (DM). Traditionally, glycosylated hemoglobin (or A1C) has been used as the gold standard measurement of glycemic control; however, there is a significant percentage of complications riskassociated with the evolution of diabetes that is not fully explained by this single marker. Short and long-term glycemic variability has been postulated as one of the main variables that contribute to increase that risk.
Objectives
To determine if there is an association between any parameter of measurement of short and/or long-term glycemic variability with the risk of developing severe hypoglycemia and retinopathy.
Material and methods
A case-control study was performed, with descriptive and analytical aspects on 103 type 1 DM patients controlled by self-monitoring of capillary blood glucoseusing glucometers with bolus calculator. Patients are being treated in the Hospital Clínico Lozano Blesa's Endocrinology and Nutrition Department. Glycemic variability data has been collected from the download of glucometers and from the A1C values obtained in successive blood tests. Statistical analysis was performed with Mann-Whitney U test, χ^2 test and

Fisher's exact test. The statistical significance has been accepted for values of $P<0.05$.
Results
A lower mean BMI (22.25 vs 25.90 kg/m^2, P 0.016) and a higher standard deviation of blood glucose mean (81.3 vs 68.6 mg/dl; P 0.003) were observed among patients with severe hypoglycemia, and there were more episodes of severe hypoglycemia in those patients with an unfavorable Clarke test (4 vs 0; P 0.035). On the other hand, the average patients' age (47.89 vs 37.43 years; P 0.001) and the time of evolution of diabetes (36.64 vs 15.42 years; $P<0.001$) were higher among those patients with retinopathy, but not the age of onset of DM (11.26 vs 22.19; P 0.001) nor the C-peptide value (0.052 vs 0.251 ng/ml; $P<0.001$).
Conclusions
Severe hypoglycemia is more frequent among patients with greater short-term glycemic variability (defined as the standard deviation of mean glycemia) while no association has been observed with any measure of long-term variability. In opposition, retinopathy has not shown an association with any parameter of glycemic variability.

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AEP521

Baseline characteristics of a cohort of type 1 diabetes patients on continuous subcutaneous insulin infusion therapy. Evaluation of glycemic variability parameters and complications.

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Introduction
Glycemic variability (GV) has been associated, regardless to A1C levels, to chronic complications of diabetes mellitus (DM).
Objective
To describe baseline characteristics, GV parameters, and microvascular complications rates in a selected simple of type 1 diabetes patients (T1DM) on continuous subcutaneous insulin infusion (CSII).
Methods
We performed a retrospective observational study with 130 T1DM patientson (CSII). Time in range (TIR) was defined as the % of time of glucose levels between 70–180 mg/dl. Low glycemic variability was defined if the coefficient of variation (CV) was lower than 36%. Data of the three previous months from the insulin pump were downloaded and analyzed.
Results
The mean age was 37±13 years-old. 51.5% were female and 19.3% of smokers. Mean BMI was 24.8±4.0 kg/m^2. Duration of T1DM was 21±10 years. Mean duration of CSII therapy was 6.3±5.4 years. The mean HbA_{1c} was 7.1±0.8% and the mean HbA_{1c} before CSII was 7.4±1.0%. 33.8% of patients were on statins, with a mean LDL-c of 100±26 mg/dl. The prevalence of diabetic retinopathy (DR) was 20.8% (95% CI : 14.7–28.5), of whom 19.2% had non-proliferative retinopathy and 1.5% had proliferative retinopathy. The prevalence of diabetic nephropathy (DN) was 10% (95% CI : 5.9–16.36), of whom 77% had microalbuminuria and 23% macroalbuminuria. 24.6% (95% CI : 18.0–32.7) presented cardioautonomic dysfunction. Regarding GV: mean TIR was 60±14%, mean time in hyperglycemia-TIH (>180 mg/dl) was 32±14%, and mean time in hypoglycemia-TIh (<70 mg/dl) was 8±7%. After applying the stepwise logistic regression model ($P<0.001$, $R^2=0.561$), we observed that the association factors for developing DR were LDL-c, ExpB 0.973 (95% CI 0.948–0.999); duration of DM, ExpB 1.256 (95% CI 1.123–1.405); and HbA_{1c} before CSII, ExpB 2.243 (95% CI 1.168–4.309). The association factors for DN ($P<0,001$ y $R^2=0.234$) were LDL-c ExpB 0.96 (95% IC 0.94–0.99) y DBP ExpB 1.11 (95% IC 1.03–1.19), and finally, the only factor for CAN was age (ExpB 1.1 95% CI 1.04–1.15). 13.84% of patients got the combined objective of $HbA_{1c}\leq7\%$, TIR ≥70% and TIh ≤10%. 54% of patients had $HbA_{1C}\leq7\%$ and CV ≤36% altogether.
Conclusion
Around half of our patients were on quite good control according to GV parameters, and had less DR and DN comparing to the T1DM general population on multiple injections insulin therapy, despite the long duration of the disease.

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AEP522

The role of tau-protein in the diagnosis of cognitive impairment in diabetes

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Diabetes mellitus (DM) is a metabolic disease, which is accompanied by systemic damage to organs, including the central nervous system. Clinically, these changes are associated with cognitive impairment, the pathogenesis of which is also largely heterogeneous.
Objective
To evaluate the role of tau-protein in the diagnosis of cognitive impairment in patients with type 1 and type 2 diabetes.
Materials and methods
The study was tested in the ethics committee, all patients signed an informed consent. Research design – observational, transverse, one-stage. The study included 126 patients with type 1 diabetes, the average age of which was 29.1±8.5 years and a control group of 25 people were comparable by sex and age. In addition, 204 patients with type 2 diabetes at the age of 60.8=11.9 years were examined, the control group consisted of 20 people comparable by sex and age. Patients were evaluated for blood glucose, hemoglobin A1c (HbA1c), and the level of tau-protein. Cognitive function was tested using the Montreal Cognitive Impairment Scale (MoCA). To assess glucose variability, we continuously monitored glycemia with an estimate of the coefficients.
Results of the study
Patients with type 1 and type 2 diabetes had cognitive impairment of 22.3 (20–25) and 21.3 (19–24) points according to the MoCA test).The clinical spectrum of disorders varied depending on the type of diabetes. When assessing the level of tau-protein, a significant increase in its content was recorded among patients with type 1 and type 2 diabetes ($P=0.001$, $U=113.0$; 0.001; $U=11.0$). Correlation analysis showed a positive relationship between tau-protein and fasting glycemia, glycated hemoglobin and the MoCA test; in addition, in the type 2 diabetes group, a correlation of tau-protein level with the presence of cognitive impairment and the age of patients was found. Significant associations of the coefficients of variability and communication with tau protein were detected only in the group with type 1 diabetes.
Conclusion
Cognitive impairment in diabetic patients is associated with taupathy and chronic hyperglycemia.

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AEP523

Diabetic muscle infarction: A life changing diagnosis with poor long term prognosis

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A 64 year old Caucasian man with long standing type 1 diabetes and complications of retinopathy, neuropathy and nephropathy was referred with suspected deep venous thrombosis (DVT) in the left lower limb. He had a week's history of worsening pain and swelling in the medial left thigh and struggled to weight bear on that leg. He felt unwell a day before admission and was found to have hyperosmolar hyperglycaemic state with ketosis on admission. Ultrasound Doppler was negative for deep venous thrombosis. T2-weighted magnetic resonance imaging (MRI) with gadolinium contrast demonstrated hyper-intense signal in the adductor compartment of the left thigh muscles. He was diagnosed to have diabetic muscle infarction and was managed with analgesia, bed rest, slow intravenous fluids, aspirin and statin. Rigorous glycaemic control was achieved with intravenous insulin. His pain and swelling improved in two weeks and he was discharged home.
Diabetic muscle infarction, also known as diabetic myonecrosis, is a serious but under-diagnosed complication of long standing diabetes. Although most patients recover from the acute episode with conservative management, the recurrence rate is high. Most patients have diabetes related microvascular complications and there is a high rate of mortality and morbidity due to microvascular and macrovascular disease. Timely diagnosis

and early involvement of the diabetes team can avoid unnecessary invasive investigations in many cases thereby improving outcomes and shortening hospital stay.

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AEP524

The connection between dopamine activated AVP release regulation and sugar substitutes

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The human homeostasis is determined by psycho-neuro-endocrine-immuno processes. This biological balance-system depends on their communication of direct environment (eg. nutrition, respiration, etc. as in the metabolism). The basic of human communication-way with environment are defined by nutrition. This contains various agents: eg. proteins, lipids, sugars, vitamins, ions, etc. When the elements of nutrition is substituted, the markers of homeostatic processes and regulations are needed to follow. In this work our aim was to investigate the AVP mediated neuroendocrine regulation, by sugar (erythritol, saccharin, xylitol, stevia) substitutes. In the experiment Wistar ♂ rats were treated with erythritol*in vivo*: 0.05 g/500 cm^3, saccharin: 2.5 g/500 cm^3, xylitol: 0.05 g/500 cm^3 and stevia: 0.05 g/500 cm^3 for 16 weeks (n=5/groups). After treating, neurohypophysis were prepared from the Wistar rats for *in vitro* primer, monolayer cell culture model (NH). The tissues were digested enzymatically (trypsin: 0.2%/Sigma, Germany/ for 30 min; collagenase/Sigma, Germany/: 30 µg/cm^3 for 40 min; dispase/ Sigma, Germany/: 50 µg/cm^3 for 40 min in phosphate-buffered saline; temperature: 37°C). Mechanical dissociation was achieved with nylon blutex sieves (∅: 83 and 48 µm). Cultures were controlled for viability (>95%) by trypan blue tests,after than for function for AVP release (in aspecific and specific regulation). In the research protocol investigation was in NH models: untreated as control, treated with 10^{-6} M of dopamine (DA) and/ or sulpiridine, and then exposed to erythritol, saccharin, xylitol and stevia, during 120 min. The AVP releases of NH model were measured by radioimmunoassay. The protein content was detected by modified Lowry method. The data were analysed by ANOVA statistical program (n=6). Our results showed mild modified AVP release activity by different treatments of sugar substitutes. However the AVP release showed expressed changes in the neuroendocrine regulation, when the *in vivo* sugar supplementation was combined by *in vitro* DA stimulation. The DA receptor (R_{DA}) functions were tested by sulpiridine. Our experiments showed that the mechanisms of DA regulated AVP release were supervised by $R2_{DA}$. These processes were modulated by erythritol, saccharin, xylitol, stevia. This works was supported by EFOP-3.6.1-16-2016-00008 and EFOP-3.4.3-16-2016-00014, TAMOP-4.2.4.A/2-11/1-2012-0001.

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AEP525

Hyponatraemia in hospital care

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Introduction
Hyponatraemia (serum sodium <136 mmol/l) is associated with significant morbidity and mortality. International guidelines suggest a clear algorithm for investigation, inclusive of measurements of paired urine sodium and osmolality, thyroid function tests and a morning cortisol. The aim of this study was to prospectively investigate the assessment, management and clinical outcomes associated with hyponatraemia on hospital admission.
Methods
This prospective study was conducted from 03/09/2018-03/10/2018, and follow-up data was collected six months thereafter. Information was garnered on hyponatraemic admissions through a combined review of patient charts and the hospital's laboratory database.
Results
Of the 418 patients admitted, 75 (18%, 35 male, 40 female) had hyponatraemia, with a mean age of 74 years (S.D.=14). Eleven were excluded on the basis of a recent surgical or oncological admission. 63 (84%) had mild (130–135 mmol/l), 9 (12%) had moderate (125–129 mmol/l) and 3 (4%) had severe (<125 mmol/l) hyponatraemia. Only 4 (5%) patients had measurements of paired serum and urine osmolality and sodium, 19 (25%) of thyroid function, and 1 (1%) of morning cortisol. Only 9 (12%) were assessed by a consultant endocrinologist. 47 (63%) were taking a culprit medication (ACE inhibitor, ARB, diuretic, SSRI, SNRI, tricyclic antidepressant) on admission, 15 (32%) of which were ceased. The mean length of hospital stay was 7 days for mild, 9 days for moderate and 16 days for severe cases, and there were 2 in-hospital mortalities. Of the 73 surviving patients, 23 (31%) did not have a sodium measurement performed at discharge, and 27 (37%) were discharged with persistent hyponatraemia. Over a 6 month follow-up period, 26/73 (36%) of hyponatraemic cases were readmitted, compared with 100/332 (30%) of normonatraemic patients. Over the same period, hyponatraemic admissions had a mortality rate of 16% (12/73), while normonatraemic admissions had a rate of 4% (13/332). The difference in proportions is significant, $\chi^2(1, N=405)=16.2$, $P<0.001$.
Conclusions
Hyponatraemia was a highly prevalent condition on admission which was largely under investigated; laboratory tests recommended by current expert guidelines were underutilised, and specialist advice was rarely sought. Management was also suboptimal; significant proportions were discharged without measurement or correction of serum sodium concentrations. Hyponatraemia was ultimately associated with a 4.5-fold excess in mortality at six months post-discharge. These findings emphasise the need for the development of Irish guidelines and the introduction of electronic alert systems to improve hospital practice.

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AEP526

Triglyceride and glucose (TyG) index is an effective biomarker to identify severe acute pancreatitis

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Background
To predict severe acute pancreatitis (AP) at early stage is important to reduce morbidity and mortality. We aimed to investigate the association between the triglyceride and glucose index (TyG index) and the prognosis of acute pancreatitis.
Methods
The TyG index was calculated as the ln[fasting triglycerides (mg/dl) × fasting plasma glucose (mg/dl)]/2. Patients were then categorized into low TyG index group (<5) and high TyG index group (≥5). Multivariable logistic regression analysis was used to investigate the independent association between TyG index and the severity of AP.
Results
A total of 313 patients with AP were recruited in this study. The proportion of patients with severe AP and the percentage of intensive care unit admissions and mortality were higher in patients with high TyG index than in those with low TyG index. The hospital stay was longer in patients with high TyG index (7.9 vs 6.0 days, P=0.019) and the area under the curve of TyG index for predicting severe AP was 0.731 (95% CI 0.64–0.82, $P<0.001$). TyG index was the significant independent factor for severe AP (OR 2.59, 95% CI 1.27–5.30, P=0.009) and intensive care unit (OR 7.34, 95% CI 2.89–18.65, $P<0.001$). (Table 1)

Table 1 The association between TyG index and severe acute pancreatitis.

	OR	*P* value*	OR	95% CI	*P* value#
Gender (Male)	0.623	0.282	0.658	0.227–1.907	0.658
Age	0.995	0.664	1.007	0.976–1.039	0.667
Gallstone	0.408	0.072			
Alcohol	2.056	0.113	2.212	0.757–6.464	0.147
Smoking	1.375	0.463			
Hypertension	1.205	0.670			
Diabetes mellitus	0.926	0.877			
Body mass index	1.048	0.286			
C-reactive protein	1.036	0.154			
Procalcitonin	1.014	0.013	1.015	1.002–1.027	0.019
TyG index	2.436	0.002	2.593	1.268–5.304	0.009

* Univariate analysis was done.
# Multivariate analysis was done.
OR, odds ratio; CI, confidence interval; TyG index, triglyceride and glucose index.

Conclusion
Our findings suggest that the TyG index is an independent prognostic factor in patients with AP and may be suitable as a simple prognostic indicator for severe AP.

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AEP527

Hormonal function of muscles in acromegaly in relation to metabolic disorders

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Skeletal muscle constitutes the largest endocrine organ in human body through capability of secreting myokines, which biological activity plays a key role in energy homeostasis. Among the myokines irisin (Ir) is of particular interest, considering it's broad spectrum of protective influence on obesity and metabolic diseases development, determining therapeutical potential of this molecule. Latest studies indicate close interrelations between Ir and myostatin (Mstn), myokine that plays a principal role in muscle mass regulation. Acromegaly is a rare disease characterised by uncontrolled GH overexpression, what makes it an attractive, naturally occurring, research model for the studies of GH action. In this work GH relations with Ir and Mstn circulating levels were evaluated. The studied population consisted of 43 acromegalic patients and 39 healthy controls. Ir, Mstn, GH and IGF-1 serum concentrations were measured. Body composition was determined using dual-energy X-ray absorptiometry (DXA). Following glucose and lipid homeostasis parameters were evaluated: fasting glucose and insulin, HOMA-IR, HOMA-β, total cholesterol, LDL cholesterol, HDL cholesterol, triglicerides, atherogenic factors (Castelli I, Castelli II, AC, AIP, TG/HDL). The study group was divided into subgroups based on disease activity as well as lipid and glucose metabolism abnormalities. The results revealed decrease in Ir serum concertation in acromegaly ($P=0.02$ vs controls) What's more, Ir levels were negatively correlated with HOMA-IR ($r=-0.51$, $P=0,01$), fasting insulin ($r=-0.43$, $P=0.01$), were relatively lower in acromegalic patients with insulin resistance (IR+) ($P=0.04$ vs IR^-) and negatively correlated with atherogenic factors. GH was negatively correlated with Mstn. Our findings indicate impaired endocrine function of skeletal muscle in the stetting of chronic GH overexpression, possible role of Ir alterations in the development of glucose abnormalities as well as relation with cardiovalcular risk in acromegaly. Additionally the role of GH in a regulation of Mstn was revealed.

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Endocrine-Related Cancer

AEP528

Sarcopenia can predict response to therapy in NSCLC patients treated with PD-1 inhibitors: A longitudinal prospective study.

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Introduction
Immune checkpoint inhibitors (ICI) show promising efficacy in the treatment of a wide range of advanced cancers, butlong-term response is currently limited to a subset of patients. Sarcopenia is a condition characterized by loss of skeletal muscle mass and decreased muscle function which occurs in approximately 50% of advanced cancer patients,related to malnutrition, inflammation, and treatments.
Objective
The aim of this prospective observational study was to investigate the relationship between sarcopenia (evaluated using DXA scan) and PD-1 inhibitors outcomes, in terms of OS and PFS, in patients with advanced NSCLC.
Materials and methods
41 stage IV NSCLC patients about to start anti PD-1, were enrolled from the Policlinico Umberto I outpatient Oncology (May 2017-September 2019). Routine blood test, endocrine, inflammatory and body composition evaluation with dual-energy X-ray absorptiometry (DXA) were performed at baseline. aLM cut-offs to define sarcopenia were ≤7.23 kg/m^2 in men and ≤5.67 kg/m^2 in women. Patients were divided into two groups based on best responseusing RECIST criteria 1.1:clinical benefit(CB)group (including complete, partial response or stable disease), and progression disease (PD) group. The statistical analysis was carried out with non-parametric tests and results are reported as medianand interquartile range. Ethics Committee approval number 4946.
Results
Overall 17/41 patients (41.5%) resulted sarcopenic based on aLMscore. Specifically, a significant higher number of patients had sarcopenia in the PD group compared to CB. Nogender difference was found regarding prevalence of sarcopenia ($P=0.732$). aLM waslower in PD vs CBgroup: PD=6.11 kg/m^2 (3.8;6.4) vs CB=7.6 kg/m^2 (5.7;7.9), $P=0.046$. As a matter of fact, lean mass was lower in PD vs CB: PD=36.3 kg (13.05;40.92) vs CB=51.80 kg (39.45;52.93), $P=0.042$. Patients with sarcopenia showed significantly worse PFS (4.9 months, 95% CI : 0.0–14.1, $P=0.03$) and worse OS (10.9 months, 95% CI : 2.6–19.2, $P=0.024$) compared to subjects without sarcopenia. In addition, considering inflammatory biomarkers, patients with sarcopenia showed higher NLR ratio ($P=0.005$), higher LLR ratio ($P=0.005$), higher CRP ($P=0.021$) compared to sarcopenic patients.
Conclusions
Subjects with sarcopenia showed worse PFS and OS compared to subjects without sarcopenia. This supports the idea that sarcopenia can reflect the increased metabolic activity of more aggressive tumors, which involves systemic inflammation and muscle wasting. Furthermore, sarcopenic patients showed higher levels of inflammatory biomarkers compared to non-sarcopenic patients. Assessment ofsarcopenia may help identify patients more likely to achieve a better response to anti PD-1 in routine clinical practice.

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AEP529

An Endocrine and metabolic interactomic approach to identify novel diagnostic/prognostic biomarkers and therapeutic targets in gliomas

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Gliomas are a common tumor type that affects the glial cells with common features of malignant tumors such as aggressive invasiveness, malignant transformation and vascular proliferation through the central nervous system. Currently, standard therapeutic strategies to treat malignant gliomas are not efficient having alow-rate survival (~12 months). Hence, there is a clear necessity for the identification of novel diagnostic/prognostic tools and therapeutic strategies to manage and treat these devastatingtumor pathologies. In this sense, a relevant relationship between metabolic/endocrine factors and tumor development/progression has been widely reported since defects in endocrine and metabolic homeostasis underlie many common human diseases, including tumor progression. In this context, we carried out an interaction omics-based approach to identify potential endocrine/metabolic biomarkers with diagnostic, prognostic and/or therapeutic potential in low- and high-grade gliomas. For that purpose, we analyzed the correlation among radiological data, IDH1/2 mutations, gene expression profiling of multiple endocrine/metabolic elements in 25 tumor biopsies samples from patients (Age 48±10-years/72%-men) clinically diagnosed with glioma (WHO2016). Initially, we used high resolution ^{31}P and ^{1}H magnetic resonance spectroscopy (MRS) in order to obtainthe quantification of 19 metabolites with a LCModel, while gene expression profiling was performed using qPCR of 19 genes related to energy metabolism. Moreover, IDH1/2 common mutation (IDH1R132H/IDH2R172H) was verified by immunohistochemistry and Sanger sequencing. Sequentially, all data was integrated using the mixOmics (R-package) allowing to build correlation network plot graphs and correlation maps to identify the most significant interactions, that were analyzed thereafter. Our results shown that the most frequent clinical features were intracranial hypertension and focal deficit. Remarkably, we found no differences between the metabolic or gene expression profiles in grade III vs IV glioma samples. However, there was a statistical significance or near-threshold correlation between some endocrine/metabolic patterns and IDH-mutation, where Alanine (4.7±1.3% IDHw vs 2.5±0.7 IDHmut), Glycine (2.7±0.5% vs 1.6±0.4%), Glycerophosphorylcholine (3.9±0.4% vs 6.4±0.9%) and Myo-inositol (4.9±1.0% vs 11.9±2.1%) were the most important biomarkers. Over expression of Lactate Dehydrogenase subunit-B (LDHB, 19±3% vs 31±6%) and Aconitase-1 (ACO1, 0.5±0.1% vs 1.2±0.3%) had also a significant or near-threshold relationship with IDH-mutation. Altogether, these results indicate that the endocrine-metabolic interaction patterns analyzed by this novel interactomic approach could be a useful tool to improve our knowledge of glioma behavior as well as being a potential source to identify novel biomarkers and therapeutic targets in order to tackle this pathology.

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AEP530

Reversal effect of Vitamin D (VitD) on exosome-mediated everolimus resistance (EveR) in hepatocellular carcinoma (HCC) cell line: A molecular study

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Cancer exosomes emerged as important mediators of cancer drug resistance. Drug exposure-mediated EveR in HCC cell lines can be reversed by VitD pre- and co-treatment. The current study aimed to investigate whether cancer exosomes from EveR HCC cell line are able to induce EveR in parental cells and whether VitD may activate reversal effect on exosome-mediated EveR. To this purpose, parental JHH-6 and EveR JHH-6 cell line were used. The uptakeof exosomes, staining with membrane dye PKH67, has been evaluated using immunofluorescence (IF). Recipient parental JHH-6 cells were treated for 16 days with exosomes from EveR cells (Exo EveR parental JHH-6) and cell proliferation was evaluated by DNA assay in parental, EveR and Exo EveR parental JHH-6 cells after treatment with everolimus (EVE) at escalating doses (from 10^{-11}M to 10^{-7}M) for 6 days, with and without VitD 10^{-7}M at lowest EVE concentrations used to better visualized the drug effect. Intracellular c-MYC and YAP-1 protein regulation was investigated by western blot (WB) after 6 days of VitD treatment in parental JHH-6, EveR JHH-6 and Exo EveR Parental JHH-6. JHH-6 parental cells were able to uptake exosomes from EveR JHH-6 cells within 18 hrs as shown by IF. Exosome's uptake conferred EveR to parental JHH-6 cells. This effect was visible in particular at lowest EVE concentrations. Treatment with EVE 10^{-10}M induced 19.76% of inhibition ($P=0.05$ vs control) in parental JHH-6 but no significant inhibition in EveR JHH-6 and Exo EveR parental JHH-6; EVE 10^{-9}M induced 56.53% ($P=0.0001$ vs control) in parental JHH-6, 26.11% of inhibition ($P=0.05$ vs control; $p=0.05$ vs EVE 10^{-9}M in parental JHH-6) in Exo EveR parental JHH-6 but not in EveR JHH-6. VitD alone induced 50.19% of inhibition ($P=0.0001$ vs control) in parental JHH-6 but no significant inhibition in EveR JHH-6 and Exo EveR parental JHH-6, while co-treatment of VitD with EVE 10^{-11}M and 10^{-10}M induced 54.78%, 56.09% and 29.61% of inhibition ($P=0.0001$ and $P=0.01$ vs EVE 10^{-11}M alone) and 28.06%, 25.37% and 38.60% of inhibition ($P=0.01$, $P=0.05$ and $P=0.0001$ vs EVE 10^{-10}M alone)in parental, EveR and Exo EveR parental JHH-6, respectively. Moreover, EveR and Exo EveR parental JHH-6 showed c-Myc and YAP-1 protein upregulation compared to parental JHH-6 but 6 days VitD treatment downregulated their expression. In conclusion, these preliminary data demonstrated that VitD may regulate exosome-mediated drug-resistance mechanisms in JHH-6 cell line, although these mechanisms need to be confirmed in other HCC cell lines.

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AEP531

Diazoxide-induced diabetic ketoacidosis in a patient with insulinoma

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Introduction
Although the first-line treatment of insulinoma remains to be surgical resection, medical therapy is necessary for non-localizable or non-resectable tumors, poor surgical candidates, or when surgery is declined. We present an interesting case of a patient with well-controlled insulinoma on diazoxide for 5 years who presented acutely with diabetic ketoacidosis (DKA).
Case presentation
A 85-year-old female presented to the Emergency Department with 2 days of severe vomiting associated with poor oral intake, generalized weakness, polydipsia and polyuria. For the last 5 years, she was compliant with low dose diazoxide with generally good control of her insulinoma. There was no fever, diarrhea, or abdominal discomfort. She reported unintentional weight loss over 4–5 months as well as polyuria for about 2–3 weeks. On examination, she was hypotensive and tachypneic but afebrile. With a plasma glucose of 57.9 mmol/l, high anion gap metabolic acidosis (pH 7.17, bicarbonate 9 mmol/l), ketonuria and ketonemia, and a calculated effective serum osmolality of 304 mOsm/kg, she had diabetic ketoacidosis with hypovolemic shock and severe acute kidney impairment (Creatinine 399 umol/l). She was treated with fluids, intravenous insulin, and cessation of diazoxide, leading to resolution of DKA within 2 days, and normalisation of renal impairment after 5 days. There were no clinical evidence of any acute precipitating factors apart from diazoxide use. Further history revealed that she had a recent admission 3 weeks ago for a rare event of symptomatic hypoglycemia despite compliance to diazoxide. Her diazoxide dose was increased from 100 mg to 300 mg, which precipitated hyperglycemia and acute kidney injury. There were no clinical evidence to suggest a metachronus change in the insulinoma to glucagonoma. There was no necrolytic migratory rash, and serum glucagon concentration was appropriately suppressed during hyperglycemia. MRI of the pancreas also showed that the insulinoma was stable in size at 6 mm without new nodules in the pancreas or liver. Her diazoxide dose was reduced to her usual dose and she did not have further recurrence of hyperglycemia at 1 year of review. In view of her old age and comorbidities, she declined surgical intervention for insulinoma
Conclusion
Diazoxide is a non-diuretic renally-cleared benzothiadiazine derivative that binds to ATP-dependent potassium channel on the beta-cell, hence inhibiting calcium influx and exocytosis of insulin. Patients on diazoxide are at risk of DKA and care should be taken to avoid diazoxide toxicity, especially in the elderly.

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AEP532

Atypical multiple endocrine neoplasia: A case report

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Background
Multiple endocrine neoplasia (MEN) are rare and are characterized by the association of a neoplasia or hyperplasia of at least two endocrine glands. Rare cases of atypical MEN were reported in the literature. We describe a rare combination of acromegaly, papillairy thyroid carcinoma and primary hyperaldosteronism.
Case presentation
We report a case of a 48-year old woman operated for papillary thyroid carcinoma. Five years later, she was diagnosed with acromegaly on the basis of typical clinical and hormonal characteristics (IGF1 plasma level of 836.7 ng/l and GH plasma level >103.8 mUI/l). The pituitary MRI revealed a pituitary macroadenoma of 20 mm of diameter invading the cavernous sinus, the posterior pituitary gland and the pituitary stalk. During the hospitalization, she presented high blood pressure and hypokalemia. A primary hyperaldosteronism was confirmed by a high aldosterone level and a high aldosterone to plasma active renin ratio. The CT scan showed a 13 mm adrenal adenoma. The association of papillary carcinoma of thyroid, acromegaly and primary hyperaldosteronism allowed retaining the diagnosis of MEN. The investigations for other endocrine neoplasia were negative. The patient was operated for the pituitary macroadenoma and was treated by spironolactone for the Conn's adenoma pending the acromegaly's control.
Conclusion
We have described an uncommon case of three endocrine tumors: acromegaly, papillary thyroid carcinoma and Conn's adenoma. This combination could be part of the MEN1 syndrome or due to the mitogenic effect of the GH-IGF1 hyperactivation.

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AEP533

Follow-up case report of an endoscopic ultrasound-guided ethanol ablation: An alternative option for the treatment of pancreatic insulinoma

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Insulinomas are predominantly benign pancreatic neuroendocrine tumors presenting with hyperinsulinemic hypoglycemia. Patients with significant hypoglycemic episodes can pose a management challenge. Based on the extent and the aggressiveness of the disease patients may be offered different treatment regimens. Although surgical resection is currently the standard treatment for pancreatic insulinoma, alternative treatment options, such as endoscopic ultrasound-guided fine needle injection may be necessary for symptomatic patients who are not candidates for surgical resolution. We present the follow up history of a now 88-year-old woman who presented with a 10 year history of fasting hypoglycemia in 2013 and was diagnosed with an insulinoma. Considering her age and comorbidities, instead of surgical intervention she was started on diazoxide treatment. Later that year she underwent ultrasound-guided alcoholic ablation of her neuroendocrine tumor, the first such procedure reported in the Hungarian literature. After the intervention she did not require diazoxide therapy for a year. Because of the recurrence of asymptomatic fasting hypoglycemic episodes, diazoxide therapy was restarted at the end of 2014. She was hypoglycemia-free until the end of 2019, when she got admitted with repeated hypoglycemic episodes occurring during the night, despite diazoxide therapy. Endosonography revealed the progress of her pancreatic insulinoma and laboratory studies showed fasting hypoglycemia with hyperinsulinemia. Because of the continued high risk of surgical resection, the decision was made to proceed with another endoscopic ultrasound-guided alcohol injection. Following the intervention the patient was discharged without diazoxide therapy and did not show hypoglycemic tendency. This case history confirms that endoscopic ultrasound-guided alcoholic ablation can be a successful minimally invasive alternative treatment for patients with pancreatic neuroendocrine tumors in whom surgery is not feasible. Our case highlights that the major limitations of ultrasound-guided ethanol ablation are the possibility of late recurrence that would require retreatment, incomplete ablation and the risk of progression during the follow-up.

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AEP534

Diverse regulation of HIF-1 on VEGF in renal cell carcinoma

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The clear cell renal cell carcinoma (ccRCC) can be sporadic or familiar, with the mutated von Hippel-Lindau (VHL) gene. The inactive VHL protein prevents degradation of hypoxia inducible factor (HIF) that promotes overexpression of angiogenic factors such as vascular endothelial growth factor (VEGF) and erythropoietin (EPO). Sequencing and multiplex ligation-dependent probe amplification (MLPA) of VHL gene in 43 samples of ccRCC in tumors vs surrounding healthy tissues revealed 27 somatic mutations. Further, testing the loss of heterozygosity (LOH) among 27 samples showed 23 biallelic and 4 monoallelic alterations in *VHL* gene. We detected an increase in VEGF mRNA and protein with a low HIF-1 gene expression in ccRCC compared to healthy tissue. To observe HIF-1 induction of VEGF mRNA, we examined tumors without or with VHL mutation (monoallelic and biallelic). In comparison to normal renal tissue, we observed a significant induction of VEGF mRNA expression in wild type tumor samples with a progressive increase in samples with monoallelic and biallelic inactivation of VHL. The human RCC 786-O cell line, a model with biallelic inactivation of *VHL*, demonstrated significant proliferation after 48 h at 21% and 3% oxygen. The human RCC Caki-1 cell line, a model with a wild type *VHL*, showed very slow proliferative effect at normal and low oxygen tension compared to 786-O cells, with significant changes after 48 h at normal oxygen tension and 10% FBS. HIF-1 protein expression was increased at low serum at 21% and 3% oxygen, both in 786-O and Caki1 cell lines. VEGF protein expression was generally low at 3% oxygen tension in 786-O cells, while it was induced at 3% and 21% oxygen after 24 h and 48 h, respectively at 10% FBS in Caki1 cells. Inactivation of *VHL* stimulated VEGF protein expression in RCC tumor tissues, but not in 786-O cell line. Hypoxia stimulated both VEGF and HIF-1 protein expression in Caki1 cell lines, regardless of *VHL* inactivation. Our data suggest diverse regulation of HIF-1 on VEGF, depending on VHL alternation, hypoxia and nutrition situation in tumor and RCC cell line.

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AEP535

Endocrine related immune adverse events associated with programmed death ligand-1 (PD-L1) therapy in hematologic malignancies: A retrospective analysis

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Background
PD-L1 represents a novel class of drugs for treatment of a broad spectrum of malignancies including onco-hematologic diseases. This treatment is associated with several immuno-related adverse events (irAEs). Thyroid diseases and diabetes are among the most common PD-L1 endocrine-irAEs reported in solid cancers.

Aims
To describe the frequency, the onset and the characteristics of PD-L1 endocrine-irAEs in patients with hematologic malignancies.
Materials and methods
We retrospectively collected data of 62 patients with lymphoma, attending the Institute of Hematology Seràgnoli of Bologna between June 2014 and August 2018, treated with PD-L1 (Nivolumab or Pembrolizumab) according to the Authority-approved doses and administration. All patients underwent metabolic and hormonal exams before the initiation of PD-L1 and during follow-up.
Results
Of 62 patients (median age: 29 years, range: 16–68), 18 affected by Nodular Sclerosis Hodgkin Lymphoma (NSHL) were treated with Nivolumab, 26 and 18 affected by NSHL and Primary Mediastinal B-cell Lymphoma, (PMBCL) respectively were treated with Pembrolizumab. All patients were followed for a median of 112 weeks (range: 4–270). The total frequency of PD-L1 endocrine-irAEs was 8.1%, characterized by only thyroid diseases. Four (2 NSHL and 1 PMBCL on Pembrolizumab, and 1 NSHL on Nivolumab) developed sudden-onset hypothyroidism at different times (from 16 to 44 weeks after PD-L1 starting). One NSHL on Pembrolizumab had an initial thyrotoxicosis at 6 weeks turning to overt hypothyroidism after 9 weeks. All 5 subjects were asymptomatic. Two of them had positive anti-thyroid autoantibodies (anti-thyroid peroxidase and anti-thyroglobulin), whereas none had detectable anti-TSH receptors. All hypothyroid subjects started l-tyroxine therapy. None of the patients developed diabetes. At the last follow up, of the 5 patients with endocrine-irAE, 3 showed complete remission and 2 disease progression of the lymphoma. No correlations were found between the endocrine-irAEs and previous oncologic therapies ($P=0.081$), and tumour outcomes ($P=0.278$ for best response to Pembrolizumab; $P=0.921$ for the last response to Pembrolizumab; $P=0.278$ for deaths).
Conclusion
The frequency of PD-L1 endocrine-irAEs in this cohort of hematologic malignancies was lower than those reported for solid cancers, and only characterized by thyroid disease. Unexpectedly, no case of PD-L1 inducing diabetes mellitus was shown. As for solid tumours the onset of endocrine-irAES was extremely variable and no correlation with tumour outcome was found.

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AEP536

Real medical challenges in the diagnostic of gastrinomas

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Introduction
Chronic hypergastrinemia is no longer an uncommon phenomenon. Zollinger-Ellison syndrome [ZES], chronic atrophic gastritis [CAG] type A, proton pump inhibitors [PPI] therapy, or Helicobacter pylori-induced CAG type B are causes of hypergastrinemia. Serum gastrin levels >1000 pg/ml (> 0 times the upper limit of normal) and PH gastric below 2 is the diagnostic of ZES, but two -thirds of ZES patients have serum gastrin levels below 1000 pg/ml. We present the case of a 63 years old female with a history of abdominal pain, chronic diarrhea, heartburn, vomiting, duodenal peptic ulcer. Additional evaluation revealed: chromogranin A level 6.5-fold higher (465.7 ng/ml), but under PPI therapy taken for the digestive symptomatology, thus nonspecific, hyperparathyroidism (vitamin D deficiency, normocalcemia), chronic autoimmune thyroiditis with an euthyroid phase. At referral, the patient was in mild distress due to the chronic diarrhea with a clinical evaluation showing normal blood pressure, IMC–26 kg/m^2 with pale skin.
The patient was referred to gastroenterology department, where the digestive symptomatology was responsive to higher dose of PPI (pantoprazole 120 mg/day). Endoscopic features excluded the atrophy expressed in CAG-A, while multiple proeminent sessile lesions (PFL) and superficial ulcerations were found. The biopsy of multiple ulcers (<1 cm) in the duodenum II showed the absence of Helicobacter Pylori and a histologic appearance (HA) similar to well differentiated neuroendocrine tumors. The immunohistochemistry showed the presence of chromogranin A and KI-67 positive in epithelial cells, inconclusive. A second endoscopy with biopsy of PFL was made, while the echo-endoscopy revealed another tumor around 1 cm diameter in the duodenum I with a HA suggestive for malignancy. Due to the insufficient material another biopsy was recommended. Fasting serum gastrin values were 6.5-fold higher under PPI therapy, thus nonspecific. After vitamin D supplementation, we can not exclude the primary hyperparathyroidism: normal vitamin D, normocalcemia, still a high value of PTH at 135.6 pg/ml with densitometric diagnosis of osteoporosis at the forearm without fragility fractures. The screening for MEN1 showed normal prolactin and IGF 1 levels. The control of acid output was achieved with a dose reduction of pantoprazole at 80 mg/day. Because of the lack of disponibility of 68 Gallium-DOTATATE, it was recommended to perform an Octreoscan.
Conclusion
This case raises awareness that often medical practice shows lack of correlation between clinical and paraclinical evaluation making a disease diagnostic like ZESa real challenge.

Keywords: ZES, hypergastrinemia, hyperparathyroidism, duodenal ulcers.
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AEP537

Pheochromocytoma due to TMEM127 mutation – the importance of genetic test for clinical decision

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Background
Catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla and the sympathetic ganglia are respectively referred to as pheochromocytomas and paragangliomas. The classic triad of symptoms in patients with pheochromocytoma (PHEO)consists of episodic headache, sweating, and tachycardia. Approximately one-half have paroxysmal hypertension; the rest have either primary hypertension or normal blood pressure. Clinicians should always consider PHEO when evaluating for secondary causes of hypertension, as missing this diagnosis can result in devastating complications, including death.
Clinical case
A previously healthy 53-year-old woman presented to her general practitioner with daily pulsatile bilateral frontal headaches persisting for 6 months, reporting different characteristics than her usual migraines. She complained of paroxysmal episodes of fatigue, palpitations, heat, sweating, and non-quantified weight gain in the previous months. Her past medical history was unremarkable, except for sporadic migraines since adolescence. She denied other relevant pathological medical history and had no previous hospital admissions or surgeries. She was not on regular medication or supplements. The physical examination was notable for a high diastolic blood pressure (BP) (137/106 mmHg) and a body mass index of 25.4 kg/m^2. Arterial hypertension was diagnosed, no treatment started, and she underwent investigation of secondary causes of arterial hypertension. During workup, high urinary metanephrines were detected and the abdominal MRI evidenced 2 nodular bilateral adrenal lesions. ^{18}F-FDG-PET/CT scanning revealed mild to moderateuptake in both lesions without extra-adrenal uptake, the ^{123}I-MIBG scintigraphy demarcated the right lesion as suspicious and a CT-scan confirmed the heterogeneous nodular lesion on the right adrenal gland as suspicious for PHEO. A right adrenalectomy was performed with posterior resolution of symptoms and normalization of urinary metanephrines and histology confirmed a PHEO. Genetic testing became available five months after surgery and revealed a TMEM127 gene mutation detected in heterozigoty (NM_017849.3:c.410-2A>C p.?).
Discussion
TMEM127 is a negative regulator of mammalian target of rapamycin effector proteins, which promote cell growth and protein translation. Due to the high prevalence of multicentric and bilateral tumors and also renal cell carcinoma in TMEM127-related PHEO, periodic surveillance of the surgical site and the contralateral adrenal gland is mandatory. Moreover, cortical-sparing procedures should be favored in order to preserve adrenocortical function. This case report evidences the benefit of genetic testing for an accurate clinical management and treatment of patients and mutation carriers in TMEM127-related PHEO.

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AEP538

Functional and morphologic response to somatostatin analogues of a pancreatic gastrinoma with unusual presentation

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Introduction
Gastrinoma is rare gastrin-secreting neuroendocrine tumor (NET), usually located in the pancreas or duodenum. The most common presentations of gastrin secreting tumor is Zollinger-Ellison Syndrome (ZES). Only about 10% of patients have non demonstrable ulcer.
Case presentation
A 67 years old female, with premature menopause, mild hypothyroidism with optimal replacement treatment, osteopenia and history of chronic gastritis, is admitted to our clinic accusing debilitating diarrhea (10 episodes/day), about 1 year before presentation. Clinical examination was normal, excepting abdominal tenderness. Carcinoid syndrome was suspected, and neuroendocrine tumor markers were measured, revealing high levels of gastrin (5× upper limit of normal) and Chromogranin A (CGA). Neuron Specific Enolaze, Serotonin and urinary 5 hydroxyindoleacetic acid were normal. Prolactin, PTH and calcium levels were normal. Also Thyroid function was normal. Upper endoscopy performed before admission did not reveal any gastric or duodenal ulcers. Classic imaging testing (CT and MRI) revealed no images suggesting a neuroendocrine tumor, but showed an adrenal incidentaloma. Lab test revealed normal values of ACTH, Cortisol, Dehydroepiandrosterone Sulfate, plasma Metanephrines and Normetanephrines, Rennin and Aldosterone. SPECT-CT somatostatin receptor scintigraphy (SRS) with 99 mTc-Tektrotyd was performed, and revealed high accumulation in the head and uncinate process of the pancreas. She was referred for surgical evaluation, but the tumor was considered inoperable. Somatostatin analogues (SSA) treatment was started in association with proton pump inhibitors (PPI) and sucralfate. At the 3 months follow up the patient presented with improvement of symptoms (3–4 normal stools/day). Also lab test revealed normalisation of gastrin and CGA. SRS with 99 mTc-Tektrotyd was repeated and revealed significant shrinkage of the tumor. Due to SSA treatment patient developed secondary diabetes mellitus, and was started on metformin.
Conclusion
Although ZES is the most common presentation of gastrinoma, 10% of patients do not present typical symptoms. Despite the fact that surgical treatment is the only curative treatment, SSA analogues is a viable treatment option in selected cases, especially when surgery is not possible, and may lead to improvement of symptoms and also induce morphologic and functional response.

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AEP539

Involvement of the splicing machinery in the antitumoral actions of metformin in prostate cancer

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Metformin has recently emerged as a potential therapeutic tool for different tumour pathologies, including prostate cancer (PCa)[1], one of the leading causes of cancer-deaths in men worldwide. However, the molecular mechanisms underlying the antitumor effects of metformin in PCa are not fully elucidated. In this context, previous reports have suggested a relationship between metformin and the process of alternative splicing in some cell-types. Nevertheless, the potential role that the splicing machinery [spliceosome components (SCs) and splicing factors (SFs)] might play in the antitumor effects of metformin in PCa remains unknown. Therefore, the aim of this study was to examine the effects and implications of metformin on the expression levels of key splicing machinery components and splicing variants in PCa. Specifically, expression levels of 14 SCs and 28 SFs were measured by a microfluidic-based qPCR array in androgen-dependent and -independent PCa-derived cell lines (LNCaP and PC-3, respectively) and in PC-3-induced xenograft tumours under low- and high-fat diets conditions in response to metformin (5 mM *in vitro*; 250 mg/kg/day *in vivo*). Moreover, different mechanistic (qPCR/Western-Blot) and functional (cell-proliferation) assays in response to metformin and/or in response to the silencing of certain SCs/SFs (using specific siRNAs) were implemented. Metformin reduced the expression level of 21% (3/14) of the SCs and 43% (12/28) of the SFs studied in LNCaP and PC-3 cells. Likewise, downregulation of certain SCs and SFs in response to metformin treatment was also observed *in vivo* in PC-3 induced xenografts. Interestingly, some of these changes were diet (low-fat vs high-fat) dependent, while others were diet-independent. Remarkably, three elements of the splicing machinery (*NOVA1, SF3B1* and *SRRM1*) were consistently reduced in response to metformin in both *in vitro* and *in vivo* models. In fact, silencing of these three elements completely blocked the anti-proliferative actions of metformin in PCa cells. Consistently, metformin reduced the expression levels of certain splicing variants related to PCa development or aggressiveness (e.g.: *KLF6-SV1*, *RAC1B*, *SST_5TMD4*) in PCa cells. Finally, we evaluated whether these changes exerted by metformin were AMPK-dependent or -independent using adenoviruses encoding either a dominant-negative or constitutively-active isoform of AMPKa. Altogether, our results suggest that the antitumor effect exerted by metformin in PCa might be mediated, at least in part, by the modulation of certain splicing machinery elements (*NOVA1/SF3B1/SRRM1*) and splicing variants(*KLF6-SV1/RAC1B/SST_5TMD4*).

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AEP540

Hyponatremia and dermatomyositis as the first manifestations of small cell lung cancer

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Introduction
Dermatomyositis is an inflammatory connective-tissue disease, characterized by inflammation of the muscles and the skin. It is more frequent among women and in 25% of cases it is related to malignancy, such as ovarian, breast, colon cancer, melanoma, non-Hodgkin's lymphomas, lung cancer, myelo-hyperplastic syndromes, and nasopharyngeal cancer. In 1/3 of cases dermatomyositis precedes malignancy, in 1/3 they present simultaneously, and in the remaining 1/3 of cases it occurs after the diagnosis of malignancy. A common paraneoplastic syndrome caused by ectopic hormone production is hyponatremia, which occurs in 15% of SCLC patients. Patients frequently but not always experience a decline in sodium level at relapse, making declining sodium a tumor marker for cancer progression, although this has not been prospectively studied. Small studies have suggested that hyponatremia is associated with shortened survival and it is poor prognostic factor for patients with SCLC.
Case report
A 67-year-old woman admitted to our hospital on August 23rd, 2019, due to severe hyponatremia. The patient was diagnosed with Dermatomyositis one month earlier, according to the results of the following physical, laboratory, EMNG examinations and biopsies. For the last 2 years, the patient was referred to the pulmologist due to productive cough, chest tightness and shortness of breath. A CT scan of the chest was performed in Mart 2019, which showed no significant changes.
Clinical findings on admission
Punctuate red rashes scattering on the face, chest and extremities, difficulty swallowing, proximal muscular weakness were noted. Pulse oxygen saturation (SPO_2) was 85%, BP 100/60 mmHg without orthostasis, pulse 86/min. She had no edema or ascites. Laboratory findings: TSH 1.45 mIU/l, cortisol 546 nmol/l, blood urea 4,0 mmol/l, creatinine 38 mcmol/l, CK 1194 IU/l, AST 123 IU/l, ALT 46 IU/l, LDH 389 IU/l, plasma sodium (P_{Na}) 116 mmol/l, potassium 3.9 mmol/l, serum osmolality 239 mOsm/kg/H2O,

uric acid 94 mcmol/l, urine osmolality 557 mOsm/kg H2O, urine sodium (U_{Na}) 106 mmol/l. MSCT examination of the chest revealed a large tumor mass in the upper mediastinum 118×56 mm with numerous macronodular focal changes in the lung. Biopsy from mediastinal lymph nodes was performed and histopatological findings showed: Small cell carcinoma. The immunohistochemistry assay of lymph node: CK ±, Synaptophysin +, CD56 +, LCA-, Ki67 positive in 90% of tumor cells.
Numerous secondary deposits have been identified in the brain by NMR examination.
She died on 12th of September, 2019, 20 days after being diagnosed with hyponatremia.

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AEP655

Correlation of chromogranin a and standard metabolic parameters in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

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Introduction
Chromogranin A (CgA) is a major representative of the protein family named granins stored predominately in secretory granules of the diffuse neuroendocrine system. Circulating CgA serves as a biomarker of neuroendocrine tumors (NETs), but its increased plasma concentration is present in various cardiovascular, gastrointestinal, renal and inflammatory diseases. Intra-granular and/or extracellular proteolysis of CgA generates a variety of biologically active fragments, which seem to beinvolved in the regulation of metabolism (pancreastatin and catestatin), cardiovascular system (vasostatin, catestatin), innate immunity (chromacin), angiogenesis and tissue repair (serpinin). It was shown that in rat models pancreastatin promotes insulin resistance by inhibiting insulin action on glucose and lipid metabolism while low catestatin promotes hypertension. The aim of this study is to analyze correlation between CgA levels and standard metabolic indices in patients with NETs.
Materials and methods
We analyzed 20 patients (mean age 47.5±14.8 yrs) with newly diagnosed well-differentiated gastroenteropancreatic NETs (GEP-NETs), 10 women and 7 men. In all subjects we measured waist circumference (WC), blood pressure (BP), fasting glucose (FG), HbA1c, total cholesterol (TC), HDL, LDL, triglycerides (TG), CgA, glucose and insulin during 2-hour oral glucose tolerance test (OGTT). We calculated body mass index (BMI), markers of insulin resistance (HOMA-IR and Matsuda index), area under the curve (AUC) for glucose and insulin during OGTT and lipid accumulation product (LAP) as a surrogate marker of metabolic syndrome (MetS).
Results
Impaired glucose tolerance was detected in one patient, impaired fasting glucose in two patients and others (17/20) had normal glucose tolerance. Our patients had (mean±s.d.) CgA 264.9±182.1 ng/ml, HOMA-IR 2.4±1.8, Mathsuda index 4.9±2.3, LAP 66.7±36.5, systolic BP 127±5 mmHg and diastolic BP 81±13 mmHg. CgA correlated with FG (r=0.572, p=0.021), Tg (r=0.532, P=0.034), systolic BP (r=0.536, P=0.039), diastolic BP (r=0.535, P=0.040).
Conclusion
This pilot study shows that CgA could serve as a marker of initial derangement of metabolic disturbances in newly diagnosed patients with NETs.

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Environmental Endocrinology

AEP541

Bisphenols release from dental composite materials

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Resin-based composite materials have become most used in restorative dentistry as a result of continuous effort to reduce the use of dental amalgam. Since 2018, it has been banned in children under 15 years of age, pregnant and nursing women. As these materials often contain bisphenol A glycidyl methacrylate (Bis-GMA) or derived monomers, bisphenol A (BPA), known for its endocrine disrupting effects, may be released and represent a low-dose and long-term source of BPA for the human body. To evade the problem of BPA presence, its structural derivatives such as BPS, BPF, and BPAF are often used in industry. The aim of this work was to determine the maximal amounts of BPA released from Bis-GMA-containing and 'BPA-free' restorative composites, and to describe the kinetics of BPA release to methanol using liquid chromatography tandem mass spectrometry (LC-MS/MS). Bis-GMA-containing composites Charisma Classic (CC) and Filtek Ultimate (FU), and 'BPA-free' Charisma Diamond (CD) and Admira Fusion (AF) were used in this study. Specimens (diameter 6 mm, height 2 mm, n=5) were light-cured from one side (20 s, 1000 mW/cm^2), and stored at 37 °C in 2 ml of methanol which was exchanged after 1, 4, 9, 16, 35, 65, and 130 days. Bisphenol concentrations were measured using LC-MS/MS. In order to gain high sensitivity, dansyl chloride derivatization was carried out[1]. The total amounts of BPA released from 'BPA-free' materials CD (8.31±1.47 ng/g) and AF (5.18±1.30 ng/g) after 130 days were significantly lower compared with Bis-GMA-containing composites CC (146.17±6.99 ng/g) and FU (182.61±5.94 ng/g). The highest release of BPA was observed within the first day of incubation, followed by a gradual decrease. The release was still ongoing since the 35-days values at a similar daily rate until 130 days of incubation. Alternative bisphenols (BPS, BPF, BPAF) were not detected. As the total amounts of BPA released within 130 days were several orders of magnitude lower than the tolerable daily intake 4 µg/kg body weight/day, these materials should not pose a serious health risk according to the current criteria.
Reference
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AEP542

A monitoring project to study nationwide trends of endometriosis incidence for environmental purposes inFrance: First step results

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Introduction
Endometriosis is a complex reproductive disease without clear etiology, thought to be on the increase, and possibly related to endocrine disruptor (EDs) exposure such as PCBs, dioxins, phthalates, or pesticides. It is part of a national project on reproductive health indicators related to EDs in France. We aimed to build a nationwide indicator of endometriosis incidence based on routinely collected data, usable to study temporal and spatial trends for environmental purposes.
Methods
A multidisciplinary expertise gathering clinicians, epidemiologists, statisticians and experts in health data mining was composed to elaborate a strategy for tracking new cases of endometriosis from the French national health care data system. We built corresponding algorithms, using ICD-10 codes for diseases and/or medical acts and/or drugs. We performed a review of literature on the epidemiology of endometriosis and links with EDCs exposure. We analyzed the usefulness of the indicators regarding our environmental purposes.
Results
Monitoring endometriosis nationwide was only possible using hospital discharges. We built 3 indicators:
– The first one involved only diseases codes of endometriosis (N80);
– The second one involved also codes for the main surgical acts, thought to enable histological diagnosis, observed nationwide in hospital discharges (a posteriori approach);

– The third indicator was issued from an a priori approach: the experts deciding which diseases codes and acts were the most relevant to identify specific forms of endometriosis, i.e. endometriomas. For each indicator, incident cases were defined as the first stay recorded without occurrence at least in the 5 prior years. In the period 2006 to 2017, we identified nationwide 30 600, 23 600 and 7500 new annual operated cases, with indicators 1 to 3, respectively. For comparison, we estimated the annual crude incidence rate with the first indicator to 12.9/10 000, which is of the same order of magnitude as in European countries using similar methods.
Conclusion
All three indicators are usable to monitor hospital cases of endometriosis nationwide, and analyze temporal trends and spatial trends at the postcode scale for environmental purposes, to explore environmental issues that are geographically determined. The indicator one reflects the better the hospital incidence, the other ones could be used for sensibility studies. The main limits of this monitoring method are the undervaluation of the public health problem, because only hospital cases are included, and possible variations of treatment or coding. A close collaboration with clinicians is critical to overcome these limits.

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General Endocrinology

AEP543

Vasoinhibin dimerization and measurement in human sera with a new vasoinhibin elisa

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Vasoinhibin, historically also known as 16K PRL, is a peptide hormone with antiangiogenic, antivasodilatatory, and antivasopermeability effects generated by proteolytic cleavage of prolactin (PRL). The discovery of its role in diabetic retinopathy and peripartum cardiomyopathy led to the development of new pharmacological treatments and their evaluation in clinical interventional trials (ClinicalTrials.gov Identifier: NCT03161652 and NCT00998556). Recent insights into the function and three-dimensional structure of vasoinhibin revealed a structure conformed by a three-helix bundle and some degree of dimerization. To study the level of vasoinhibin dimerization and the presence of vasoinhibin in human serum, recombinant human vasoinhibin and human sera were investigated by SDS-PAGE and Western blotting, preparative electrophoresis, mass spectrometry, immunoprecipitation, and ELISA. Commercial poly- and monoclonal anti-PRL antibodies were used, and monoclonal anti-vasoinhibin antibodies, designed to specifically bind vasoinhibin and not PRL, were generated by the hybridoma technique. A sandwich ELISA for vasoinhibin was developed, using anti-vasoinhibin monoclonal antibodies. Over 90% of recombinant vasoinhibin monomers aggregated to form a 28 kDa dimer which is resistant to standard denaturating and reducing conditions and dissociated only after prolonged exposure to heat and ß-mercaptoethanol or DTT. Western blotting analysis and immunoprecipitation demonstrated the presence of a highly abundant, 28 kDa endogenous protein in human sera, with immunochemical features of vasoinhibin. The ELISA, calibrated with a recombinant human vasoinhibin-standard, had a detection limit of 39 ng/ml, a quantitation limit of 207 ng/ml, and intra-assay- and inter-assay coefficients of variation of 12.5% and 14%, respectively. Serum samples from 9 individuals were tested, and showed variable concentrations ranging from 1 to 210 µg/ml. The contribution of endogenous vasoinhibin to these measurements is under investigation.

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Expanding the clinical and genetic spectrum of 17α-Hydroxylase/17,20-Lyase deficiency: 7 cases and 5 novel mutations in the CYP17A1 gene

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Context
Cytochrome P450 (CYP) 17A1 is located at major branch points of steroidogenesis exerting two distinct catalytic activities: 17α-hydroxylase generates glucocorticoid precursors and 17,20-lyase generates the principal sex steroid precursor dehydroepiandrosterone (DHEA). CYP17A1 deficiency (17OHD) is a rare form of congenital adrenal hyperplasia. In severe 17OHD, affected individuals typically present with both glucocorticoid and sex steroid deficiency and mineralocorticoid excess due to accumulation of steroid precursors. Partial enzyme defects have been rarely reported.
Aims and objectives
To analyse the genetic and phenotypicspectrum of seven patients with 17OHD.
Methods
Urinary steroid profiling (GC-MS), sequencing analysis of the *CYP17A1* gene, *in silico* analysis utilising the crystallized human CYP17A1 protein structure (PDB: 3RUK), *in vitro* analysis employing a HEK293 cell CYP17A1 overexpression assay with quantification of steroid conversion by LC-MS/MS.
Patients and results
The clinical spectrum ranged from neonatal adrenal insufficiency with failure to thrive and conjugated jaundice toisolated sex steroid deficiency with normal blood pressure and normal serum cortisol after ACTH stimulation. We found five novel (p.Pro409Leu, p.Gly111Val, p.Ala398Glu, p.Ile371Thr and p.Tyr60Ile*fs*Lys88X), and three previously described *CYP17A1* sequence variants (p.Arg347His, p.Gly436Arg, p.Phe53/54del). *In vitro* functional analysis showed correlation of 17α-hydroxylase activity with the severity of the phenotype: the missense variants p.Ile371Thr, p.Ala398Glu and p.Arg347His, carried by patients with normal cortisol response, retained up to 14% of residual 17α-hydroxylase activity. The known variant p.Phe53/54del, found in two siblings with a moderate phenotype, retained 5.8% of WT activity. The sequence variants p.Pro409Leu, p.Gly111Val, p.Gly436Arg and p.Tyr60Ile*fs*Lys88X, carried by severely affected patients, had <1% residual 17α-hydroxylase activity. In contrast, 17,20-lyase activity was nearly abolished in all variants studied, except for p.Ile371Thr, which retained 3.6% of WT activity. A diagnostic ratio of urinary mineralocorticoid to glucocorticoid metabolites, reflecting 17α-hydroxylase activity, correlated well with both the *in vitro*17α-hydroxylase activity and the severity of the clinical phenotype. *In silico*mutant protein analysis identified conformational changes rather than disruption of co-factor binding for all variants studied.
Conclusion
Our findings expand the genetic and clinical spectrum of 17OHD. We describe novel phenotypes at both extremes of the spectrum, with severe neonatal adrenal insufficiency on the one hand, and isolated sex steroid deficiency with normal cortisol response to stimulation on the other. Importantly, attenuation of 17α-hydroxylase activity is readily detected by urinary steroid profiling in all cases, thus providing a powerful tool for the biochemical diagnosis of 17OHD.

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Mental disorders in adult patients with diencephalon lesions by craniopharyngiomas.

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The tumors of the thalamic-hypothalamic-pituitary system (diencephalon region, DR) include a fairly large group. These are pituitary adenomas, craniopharyngiomas (CP), pineal tumors, gliomas, meningiomas, and others. Tumors differ in the location, histological structure, and manifestations of the clinical picture with the corresponding hormonal changes, approaches and methods in treatment. Psychopathological symptoms are revealed in the symptoms of lesion of the DR in addition to cerebral, neuroendocrine symptoms, neurological disorders. It is represented by emotional, motivational, personal, cognitive impairments, inversion of the sleep-wake cycle, seizures.
Objective
To study of mental disorders in patients with diencephalon lesions (on a model of benign tumor of craniopharyngiomas).
Materials and methods
120 adult patients (18–68 years old, median 39 ± 2; 59 women and 61 men) who were first admitted for treatment with a diagnosis of CP (2007–2015). The main method was psychopathological; data from endocrinological, neurological, neuroimaging. CP were classified according to initial growth and relation to the third ventricle: endosuprasellar (n = 26), suprasellar (with initial growth in the pituitary stalk, with no penetration into the third ventricle) (n = 45), extra-intraventricular (n = 35) and intraventricular (n = 14). Hypopituitarism/panhypopituitarism, diabetes insipidus was detected in 89%before surgery.
Results
Mental disorders in the clinical picture of CP were detected in 103 (85.8%) patients with syndromes: emotional and volitional disorders in 79 (65.8%), memory impairment in 71 (59.1%), personality changes in 71 (59.1%), paroxysmal conditions in 55 (45.8%), sleep disorders in 54 (45%), and consciousness disorders in 24 (20%). Mental disorders do not manifest themselves in isolation, but together with each other, and therefore are superior to each other in the clinical picture or to varying degrees with various topographic and anatomical variants of CP : in 65% of cases with endosuprasellar, in 86% – with stalk, in 100% – with extra-intra- and intra-ventricular CP. The most severe mental disorders: Korsakov's syndrome, aspontaneity, akinetic mutism, personality defect were noted in 21% of cases, more often in patients with extra-intra-ventricular CP.
Conclusion
Mental disorders in the clinical picture of CP were detected in 85.8% of patients before surgery, determined by the location of the damage – topographic and anatomical variants of CP, the spread and effect of the tumor on the structures of the DR, limbic system, and III ventricle, with corresponding neuroenodcrine disorders.

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Late effects of allogeneic stem cell transplants on the endocrine and metabolic systems

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Stem cell transplants are used to treat and cure many types of haematological malignancies as well as rare solid-organ tumours. The conditioning regimes, medications and potential graft vs host disease can have effects on many organ systems in the body. The Endocrinology Department has designed a follow-up service over the past 3 years for patients in remission due to increasing awareness of the potential endocrinological and metabolic effects of allogenic stem cell transplant. This study aims to identify the effects allogenic stem cell transplant has on those systems. We retrospectively analysed patients who received bone marrow transplants in St. James Hospital between 2002 to 2018. We have analysed patients above 18 years old who have undergone stem cell transplant, attended the late effects clinic and are clinically in remission and deemed long term survivors. Metabolic and endocrinological markers such as liver function tests, glycated haemoglobin, fasting lipids, thyroid function tests, and reproductive hormones levels were obtained and measured over time. There were 412 late effects patients who had stem cell transplants between 2002 to 2018. We have analysed year one data from 100 patients who had bone marrow transplant between January 2016 to December 2019. Average age of these patients at time of bone marrow transplant are 43.6 (± 14.4) years old.2 patients had biochemical evidence of hypothyroidism. 17 had biochemical evidence of subclinical hypothyroidism. Average time of onset was 10.7 (± 4.3) months from receiving bone marrow transplant. Average thyroid stimulating hormone (TSH) at time of onset was 6.65 (± 4.33) mU/l with free T4 of 13.12 (± 4.32) pmol/l. 1 patient developed subclinical hyperthyroidism with TSH 0.04 mU/l and T4 of 21 pmol/l prior to developing hypothyroidism. There were 45 females analysed so far. 4 of those patients under 40 years old developing hypoestrogenism, all within 3 months of transplantation. 55 males were analysed with none having biochemical evidence of hypogonadism within that one year. 53 patients had deranged liver function tests with average time of onset of 7.4 (± 2.1) months. The long-term effects of bone marrow transplant on metabolic and endocrinological systems are still largely unknown. This study emphasizes the need for ongoing endocrinological support for these patients as well as further research into the long-lasting impact bone marrow transplants can have on these patients.

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Joining forces in endocrine cancer genetics

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Patient- and family center edendocrine cancer care encourages active collaboration between the departments of endocrinology, oncology, surgery, pathology, chemistry, radiology, nuclear medicine and clinical genetics. The implementation of high-throughput DNA/RNA sequencing platforms has allowed novel molecular information to be used to optimize primary endocrine cancer care including tumor classification, prognostic forecasting, stratification for targeted treatment in recurrent disease and the identification of patients at high risk for tumor development. Multiple Endocrine Neoplasia (MEN) type 1–2 and von Hippel-Lindau syndrome were among the first hereditary tumor predisposition syndromes to be recognized and over time the number of endocrine tumor syndromes and associated genes has expanded significantly. Depending on the specific endocrine tumor type, 10–30% of cases are associated with genetic factors, in which up to 15 different genes per tumor type may be implicated. The proportion of inherited disease in the context of the totaldisease population in clinical practice might be an underestimate owing to still unidentified genetic causes orbecause heredity is not recognized due to an unavailable, incomplete or misdiagnosed family history and/or variable penetrance. Identification of a causative germline mutation may not onlyhave important clinical implications for the index patient (proband), it also facilitates cascadetesting and surveillance of relatives in order to prevent, or at least allow early identification of, (pre)malignant conditions. Current challenges in known tumor predisposition syndromes include accurate estimates of variant pathogenicity, disease penetrance, genotype-phenotype relationships and the variable phenotypes within families, and from there to tailored treatment and surveillance guidelines. While endocrine neoplasia syndromes show many features commonly seen in familialdisease (early onset, family history, multifocal neoplasia, multiorgan involvement), some of these syndromes are considered to be phenotypically complex and heterogeneous. The use of whole exome sequencing for diagnostic and research purposes may lead to identification of a syndrome that was not in the initial differential diagnosis. The drawback of testing many genes is the complex interpretation of the results. Pre-test genetic counseling to establish the preferred sequence modality and tiered informed consent is therefore of utmost importance. Improving endocrine cancer genetics requires not only local, national and international collaborations between the medical disciplines involved but also the interaction between basic and clinical research, taking research from bench to beside and back again.

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Patient perception and views on quality of care for rare endocrine diseases. Results from an EndoERN survey

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Introduction
An aim of the ERNs is empowering patients, by education & learning about their experiences after diagnosis of a rare endocrine disease (RED), to identify gaps and improve outcome. Thus, EndoERN Work Package 4 designed a survey, to learn about patients perceptions on quality of care and existing gaps in diagnosis/management.
Aim
Evaluate results of a 21 question survey answered on-line on a Likert scale by individual patients with RED or support groups.
Patients and method
questions were answered in their own language, related to delay and number of professionals contacted before correct diagnosis, time to find a specialist and specific treatment, satisfaction with current treatment, information received and health care follow-up, possibility of access to specific specialist support, and if not, whether they would have liked to have this access, availability of written information on their condition, contact with patient/support groups, and impact of their condition on everyday quality of life.
Results
There were 598 responses from 25 countries (58% individual patients, 34% patient groups and 8% both); 66% were females. Data from pituitary, adrenal, thyroid, parathyroid, gonadal, genetic and autoimmune endocrine diseases were collected. While in 36% a diagnosis was made in <1 year, in 28% it took more than 5 years. In 64% it took 2 to 7 professionals to reach correct diagnosis, after which in more than half a specialist/specific treatment was available within 1 month; 60% manifested being satisfied with current treatment. As far as access to other health professionals, the majority (59 to 67%) manifested not to have had access to specific psychological support, psychologist/social worker, dietician or physiotherapist/rehabilitation specialist, but would have liked to (42 to 49%), As far as information on their condition, treatment possibilities, and degree of satisfaction with health care follow-up, around half were either satisfied or very satisfied; 53% had received written information on their condition and 87% had contacted patient/support groups; 78% declared to completely or moderately agree with the sentence 'The personal limitations related to the disease, impact on my everyday quality of life'. Conclusions: Diagnostic delay is a problem in RED, although once diagnosed, access to specific specialists and treatment was mostly <1 month. Most are satisfied with treatment despite significant impact of their condition on their lives and difficulties to access all desired health professionals. Whether these results are extensible to all European patients with RED is unknown.

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True hyponatremia – An unusual side effect of IV Immunoglobulins

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Background
Guillain-Barré syndrome is a rare but very serious autoimmune disorder and it's caused by the immune led demyelination of the peripheral nervous system. The symptoms are mainly weakness and numbness, but can also consist in severe respiratory failure due to paralysis. The treatment consist in administration of intravenous immunoglobulins (IVIGs) which shorten the duration of disease.
Case presentation
A 67 year-old man was referred to our Endocrinology team due to hyponatremia. The patient was admitted in the hospital 6 days previously due to 1-day history of hand and legs numbness and weakness. He denied any recent history of trauma to the spine Two weeks prior to this current emergency visit, he complained of flu like symptoms and upper respiratory tract infection. On admission he was alert, and not in respiratory distress. His presenting vitals were stable. Neurological: reduced tone, muscle power of 4/5 bilateral upper and lower limbs, absent tendon reflexes at the patellas and ankles, bilateral downgoing plantar response and reduced sensation to soft touch and pin prick from knee below. The cranial nerves were intact. Examination of cardiovascular, respiratory systems, abdominal and skin were unremarkable. His full blood count, renal and liver function, cardiac enzymes, blood gas were within normal limits.
Patient received 5 days of IVIGs and then the Sodium dropped to 125 mmol/l. This was considered SiADH, started on fluid restriction and referred to Endocrinology. Seen by our team 48 h later (bank holiday) – patient was stable but worsening hyponatremia.
Initial impression
Pseudohyponatremia secondary to IVIGs (this medication is known can increase plasma Osm).
Final Diagnostic
True Hypotonic Hyponatremia as further investigations revealed low Plasma Osmolality 263 mmol/kg with significant increased Urine Osmolality (687 mmol/kg) and loss sodium in the urine. The fluid restriction was stopped and for next few days the hyponatremia actually initially worsen (lowest Na 117 mmol/l) due to a very complex mechanism. The patient received iv fluids and slow salt tablets for 3 days. The Sodium level had slowly improved and remained stable. We reviewed other cases which were previously treated with IVIG. Unfortunately the data was limited but other cases of hyponatremia post IVIGs were identified.
Conclusions
We would like to highlight our case for the need to be vigil about such complications and to avoid fluid restriction in cases of patients treated with IVIGs as this can worsen hyponatremia.

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AEP550

Publication outcome of abstracts presented at European Congress of Endocrinology via web scraping and automated searches

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Background
Conversion rates of the presentations into publications could be a measure of the scientific Impact of a conference. The aim of the current study was to determine the publication rates of abstracts presented at the 16th European Congress of Endocrinology (ECE 2014) and the factors affecting these rates by using computer algorithms specially coded for this analysis.
Methods
All presentations of the ECE 2014 were collected with the web scraping – Python coding from official website and converted into the desired formats. Parameters were transformed to Google Scholar and PubMed search links with coding. A special interface was coded to evaluate the results of the three searches on the same screen and to save the results into the database. Web Scraping was coded in Python version 3.4 with the open source code/module BeautifulSoup version 4.4.0. The time frame for publication search was between May 2013 and August 2019.
Results
A total of 1205 abstracts from 71 countries were featured. Among these, 1145 (%95) were poster presentations and 60 (%5) were oral presentations. Subsequently, 341 abstracts (28.3%) were published as a full paper. The conversion rates to publication for oral and poster presentations were 65% and 26.4% respectively (OR : 5.18, 95% CI : 3.0–8.96, $P<0.01$). The median time to publication was 12 months (IQR : 2–24 months). Impact Factors (IF) of publications from oral and poster presentations were median IF of 5.0 (IQR : 3.83–5.96), and 2.94 (IQR : 1.77–3.83), respectively ($P=0.01$). Median number of citations of publications from oral and poster presentations were 12 (IQR : 6–33) and 6 (IQR : 2–15), respectively ($P=0.01$). A total of 90 (7.5%) multi-country abstracts were identified. Multi-country collaborative studies were turned into more publications than single-country studies (OR: 3.91 95% CI : 2.52–6.06, $P<0.01$). As of August 2019, a total of 3835 citations to the papers generated from ECE 2014 were identified with a median of 6 (IQR: 2–17) at the Web of Science. The congress potential impact factor was calculated as 3.18.

Table 1 Publication conversion rates according to type of studies.

	Presented (n, %)	Full Publication (n, %)
Clinical studies	739 (61.3%)	222 (30%)
Case reports	301 (25%)	49 (16.3%)
Basic/translational studies	165 (13.7%)	70 (42.4%)
Total	1205	341

Conclusion
This first study evaluating the publication outcome of ECE shows that 28.3% of the abstracts presented at the congress are published with 12 months of median time to publication.

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TNF-α induces hyperpolarization in agrp neurons without affecting pomc neurons of the arcuate nucleus

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Neurons expressing the agouti-related protein (AgRP) and the pro-opiomelanocortin (POMC) are part of the central system responsible for regulating energy balance and food intake. The hypothalamus is sensitive to changes in the inflammatory state. Either high-grade inflammation (e.g., caused by sepsis) or low-grade inflammation (caused by obesity) disturbs the hypothalamic function via inflammatory cytokines. Understanding how these cytokines interact and regulate the circuits that control energy homeostasis is critical to understanding the pathophysiology of energy balance disorders. AgRP or POMC reporter mice were used to evaluate the acute electrical effects of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) on these neurons through whole-cell patch-clamp. Our results showed that 73% of AgRP cells were active and 27% quiescent during the recordings ($n=33$ cells from 19 mice, 24 active and 9 quiescent). IL-6 (10 ng/ml) had no effect on theresting membrane potential (RPM) or membrane resistance(IR) of AgRP neurons. In contrast, TNF-α (20 ng/ml) induced a significant hyperpolarization in approximately 31.5% of registered cells (6 out of 21 neurons, change in RPM: -9.8 ± 0.9 mV; $P<0.0001$), although a non-significant reduction in the IR ($P=0.5$) was observed. Regarding POMC neurons, we found that 61% of POMC cells were active and 39% quiescent during the recordings ($n=38$ cells from 22 mice, 23 active and 15 quiescent cells). Both IL-6 and TNF-α had no significant effects on the electrical properties of POMC neurons. Therefore, these findings suggest that cytokines that are altered during sepsis or obesity may affect the activity of neuronal circuits that regulate energy balance. Additionally, the acute inhibitory effect of TNF-α on AgRP neuronal activity may explain the suppression in food intake observed during situations of high-grade inflammation.

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AEP552

The extent of variation in the reporting of clinical activity by reference centres in the field of rare pituitary and thyroid disorders within Endo-ERN, a new reference network for rare endocrine conditions in Europe

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Objective
Self-reported volume of patients and specific interventions is a specific network criterion that needs to be fulfilled by reference centres that are eligible for inclusion within Endo-ERN. The aim of the present study is to evaluate how self-reported volume data in the original applications were obtained, which data are retrievable, and which set is best suitable to use for future centre evaluations. This overview is provided for two Main Thematic Groups (MTGs) of Endo-ERN: Pituitary and Thyroid.
Design and methods
Review of application forms and continuous monitoring data of Endo-ERN and a survey distributed to participating centres. A list of 'key procedures' for the assessment of the performance of RCs was composed with the help of the chairs of the concerned MTGs.
Results
In the application forms, the variation in number of procedures ranged from 20 to 5500/year for Pituitary and from 10 to 2700/year for Thyroid). The survey response rate was 63% for both MTGs. The number of performed key procedures also varied widely. However, ranges were significantly smaller than those of performed procedures in general. The median numbers of new patients reported for the ERN continuous monitoring program (2017 and 2018) were comparable with those reported in the application and survey, however, some centres reported large alterations in the number of new patients.
Conclusions
The number of new patients, patients under chronic care, and related procedures vary widely between RCs. In addition to the size of the practice, this is also due to non-uniform definitions of new patients and procedures used by the reporting RCs. Application of uniform definitions, in addition tothe development of MTG subtheme specific performance indicators, is urgently needed. This will allow a more reliable assessment and comparison of RC and overall Endo-ERN performance.

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AEP553

'I would say this is a good clinic for friends & family to be looked after in if they need similar treatment or care' – Young Adult Endocrine (YAE) Service Evaluation

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Aim
To evaluate the current service provisions and provide action plan for improvement within the YAE service.
Methods
A friends and family questionnaire given to all patients attending the YAE service from October 2018 – January 2019. Survey questions included: whether they thought this was a good clinic for friends and family to be looked after in, what we did well and what we could do better. For YA patients transferring from children's service, additional questions included whether: they think their transfer went smoothly, if they met a member of the adult team before transfer and they know the name of someone to contact, as well aswhat we did well and what we could do better.
Results
There were a total of 111 young adults (YA), age 16–24 years old, who completed the friends and family questionnaire. 58 (52%) were aged between 16–19, 53 (48%) had transferred from children's services, 52 (47%) were attending for their first or second appointment. About 99 (88%) agreeda lot or a bit with the following statement 'I would say this is a good clinic for friends & family to be looked after in if they need similar treatment or care'. They found the staff friendly and helpful. 20 YA patients made suggestions including more wide range of leaflets, to be seen by the same consultant, exercise advice, free gym membership, more information on pregnancy issues and conduct-skype appointments. For YA patients that had transferred from children's service; 48 (90%) agree that the transfer had gone smoothly for them, 39 (74%) were aware of meeting a member of the adult team and 38 (72%) knew the name of someone to contact. 9 (17%) YA patients offered suggestions for improvements, including more support after the appointment, less confusing by speaking 'smaller' words and days where just young people come to clinic. YA patients highlighted issues with the appointment system.
Conclusions
This YAE service evaluation has demonstrated that the majority of YA patients are satisfied with the service and felt that transfer went smoothly. However, improvements are required to comply with national transition guidance and meet the needs of YA patients.

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Neurofibromatosis type 1: About two cases

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Neurofibromatosis type 1 is a genetic multisystemic disorder involving the skin, the central and peripheral nervous systems, bones, and the cardiovascular and endocrine systems. We report 2 cases of type 1 neurofibromatosis in 2 patients aged 27 and 23 years respectively. The dermatological lesions (neurofibroma and café au lait spots) were the revealing symptoms. Cerebral MRI revealed a glioma of the optic chiasm developing along the Optic nerves. NF1 has been known for 10 years in the 1st patient, the glioma is stable to differences in imaging controls, after the opinion of the neurosurgeon, radiotherapist and oncologist, simple monitoring is recommended, progress is currently favorable, the search for other lesions is negative. Concerning the youngest patient, the diagnosis of NF1 is recent, the dermatological lesions have been evolving for 3 years, in addition to the glioma, he has a cystic nodular lesion of 18 mm in the pineal region and a delay in stature and Lisch nodules, the search for pheochromocytoma is negative and the abdominopelvic CT scan is without abnormalities, the hormonal assessment is in progress.
Discussion
The gene responsible for NF1 is a tumor suppressor gene, has been located on chromosome 17 in region 17 Q 11, 2. It codes for the protein neurofibromin. Its penetrance is close to 100% at the age of 5 and de novo mutations represent around half of the cases. Neurological manifestations are frequent, exist in half of the cases. 15 to 20% of patients have tumors of the nervous system (gliomas, astrocytomas, neurofibromas). Glioma of benign histology, can sit at any level of the optic pathway, and is expressed by exophthalmos, reduced visual acuity, visual field impairment, precocious puberty by hypothalamic involvement and rarely hydrocephalus, but often asymptomatic and without progression, thus recommending a systematic ophthalmological evaluation (visual examinations, cerebral and orbital MRI) annually mainly in the population of children under 10 years of age and more widely spaced in adults. as well as a systematic search for precocious puberty. The treatment is based on chemotherapy allowing stabilization see tumor reduction. NFI is a genetic disorder responsible for disorders in the differentiation of ectodermal tissue. Despite the discovery of the gene responsible for this disease, the diagnosis remains clinical and is based on defined criteria. Progressive lesions are however very rare and their frequency is very different according to age. In the absence of clinical signs predicting these, clinical monitoring is advised.

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Invivo endocrine internet: An unique model of endocrine system

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Background
Endocrine system (ES) is unique amongst all organ systems (OS) in human body. ES is a conglomeration of different endocrine organs. So far, the only models of proof o fintegrity within ES are APUD cell concept; HPA axis; HPG axis; biochemical pathways of hormones. But, the flaws in the above models are their presumptive and extrapolative nature. We wanted to test a model that every endocrine disease has collateral effect on other endocrine organs. We took nontoxic goiter (thyroid) and primary hyperparathyroidism as prototypes.
Material and methods
This prospective case-control study was conducted on 300 cases (270 thyroid and 30 parathyroid) and age matched 300 controls from healthy blood donors over a period of 12 months. Institutional ethical committee approval was obtained. All thyroid and parathyroid cases underwent uneventful curative thyroidectomy and parathyroidectomy respectively. Exclusion criteria were subjects with any febrile illness, candidates with stress, anxiety neurosis, allergies, chronic drug use, diabetes, systemic or chronic inflammatory disease or calcium/vitamin D supplements, any medication which interferes with the normal function of the hypothalamic-pituitary axis, menopausal age group. Serum samples were collected preoperatively, from all the subjects in both groups as per the standard collection times and procedures. Statistical analysis was performed by SPSS 20.0. *P* value of <0.05 was considered significant.
Results
Mean prolactin, Luteinising hormone (LH), follicular stimulating hormone (FSH), parathormone, cortisol and testesterone in thyroid cases and controls were 28.6±8.2 ng/ml (12–87), 24.3±1.9 IU/l (10–57), 16.6±3.4 IU/l (8.4–41), 23.5±4.7 pg/ml (15–65), 7.2±2.4 mg/dl (4–16.5),256±57 ng/dl (167–478) and 14.5±3.4 ng/ml (8–18), 11.4±2.5 IU/l (2.5–12.5), 6.2±2.9 IU/l (3.5–21), 21.1±5.3 pg/ml (9–46), 11.2±3.6 mg/dl (5.5–19), 212±45 ng/dl (115–368) respectively. There was statistically significant difference of prolactin, LH, FSH and cortisol values between thyroid cases and controls. But statistical difference was significant only for prolactin, FSH and LH between parathyroid cases and controls.
Conclusions
Our study highlights an unique model of endocrine homeostasis and integrity of ES. The results provides a distinct opportunity to screen and pre-emptively treat subclinicalendocrine diseases. But, the exactpathophysiological mechanism and significance ofhormonal interplay between varied endocrine organs needs active research.
Keywords: thyroid, parathyroid, prolactin, goiter, cortisol, insulin.
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Autoimmune polyglandular syndrome (APS) type 2 associated with chronic kidney disease

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Introduction
Autoimmune polyglandular syndrome (APS) is a rare disease, that is defined by the presence of two or more glandular insufficiencies caused by autoimmune mechanisms and that may be associated with other pathologies and immunological phenomena. It is characterized by the Presence of circulating organ specific antibodies and lymphocytic infiltration of the affected gland.
Case report
A 38-year-old female known to have autoimmune polyglandular syndrome type 2. 14 years ago, she wasdiagnosed with hypothyroidism and primary adrenal insufficiency on Eltroxin 100 mg and hostacortine 5 mg. 4 years ago, she developed type 2 diabeteson insulin mixtard 34 U before breakfast and 12 U before dinner. She had secondary amenorrhea for 4 years ago. Referred from emergency department with hyperkalemia.
On examination
The patient is fully conscious, Pulse: 90 beats/minute/BP: 190/100/RR: 16–20/minute, BMI: 23.55 kg/m^2. Normal head and neck, cardic, chest, abdominal examination.
Investigation showed.
Leukocytosis (white blood cells: 14,100 cells/µl) with a neutrophil count of 84.9%), HB 13.1, normal coagulation profile, elevatedurea 79 mg/dl, elevated creatinine 1.15 mg/dl, low eGFR56 ml/mit, normal urine analysis, Albumin/Creatratio: 10 mg/mmol, normal sodium level. 135 mEq/l, hyperkaleamia (Potassium 9.7 mEq/l), normal calcium (9.2 mg/dl) normal phosphrous (4.9 mg/dl), hyperurceamia (8.3 mg/dl), arterial blood gases showing metabolic acidosis (pH: 7.31, PCo2: 33.2 mmHg, HCo3: 16.7 mmHg, Anion Gap: 12.6). Negative HCV, HBsAG. Renin >128 pg/ml(4–46)/Aldosterone 50.3 pg/ml (30–350). Thyroid profile normal (TSH: 2.82 mIU/l,FT4: 1.4 µg/dl, F T3: 91 ng/dl). Positive anti TPO. Post-menopausal FSH: 80.4 IU/l/post-menopausal LH: 84.3 IU/l. A 12-lead ECG revealed normal sinus rhythm with no hyperkalemic changes Abdominal sonar: Bilateral small sized kidneys. She sought medical advice and wasfound to have renal impairment (Creatinine 4 mg/dl then dropped to 1.4 mg/dl following hydration with IV fluids). Repeated admission with hyperkalemia resistant to anti hyperkalemic measures without any ECG changes and was placed on Kayexalate. Interstitial nephritis wassuspected however, our patient refused to do renal biopsy. Last creatinine done 1.5 mg/dl, eGFR 41 ml/mint. Here, we reported a case of APS-2 with an uncommon condition involved 3 endocrine organs (thyroid, adrenal, and ovarian) with interstitial nephritis.
Conclusion
Patient education, detailed evaluation, and long term follow up of patients and first-degree relatives for possible co-existence of diseases are the cornerstones for managing patients with APS.

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Role of endocrine specialist nurse in early inpatient discharge

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Adult endocrine specialist nursing (ESN) is a highly specialised role and in recent years nurses have expanded their roles according to local need (Kieffer.V, *et al.* 2015). As an Endocrine team we review our practice, striving to provide the highest standard of research based, patient centred care. This involves ensuring the best use of resources and service provision in an ever more demanding environment. A new initiative lead by the ESN with consultant supervision was put in place to offer, where clinically feasible on selected inpatients the option of early discharge with next day review of pending results and/or medication adjustment. Our patients were selected from acute medical wards undera Diabetes and Endocrine speciality. During 2019 the consultants identified 45 different patients who would be eligible for early discharge. They were given an appointment to return to the early discharge clinicswhich were set according to demand, Monday to Friday by the lead ESN. Of these patients 27 had an endocrine condition/s and 18 were diabetes related. Patients generally required between 1 to 3 appointments. In total 68 clinic visits were needed, which equates to freeing up a minimum of 74 bed days. Of those who attended 100% were very satisfied with the care received and the reduced length of their hospital stay.
Conclusion
Following this trial we are putting forward a business case to increase the ESN capacity, with consultant supervision, to offer the early discharge clinic to other wards. This would ensure patients are seen by the right specialist, in a timely manner, in the most appropriate environment (endocrine investigation unit). Patients will receive the best possible care while ensuring better utilisation of bed capacity and junior doctor's time which can subsequently be redirected towards ever changing demands in the hospital/s.

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Delay in diagnosis and clinical course of autoimmune polyglandular syndrome

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Autoimmune polyglandular syndromes (APS) are a rare group of autoimmune disorders that affect more than one endocrine gland, although non-endocrine organs can be involved. Concerning the variable evolution of this clinical entity over time, our case aims to emphasise the importance of regular follow-up and screening for polyglandular autoimmunity in selected patients in order to decrease a possibility of future complications consistent with APS. We report the case of a 20-year-old female presented with frequent episodes of hypoglycemia over the last 2 years, extreme fatigue, weight loss, nausea, vomiting, abdominal pain and secondary amenorrhea. She was diagnosed with type 1 diabetes mellitus (T1DM) at the age of 6 years and necrobiosis lipoidica at 9 years. Her mother has primary hypothyroidism and celiac disease while her second-degree maternal lineage was positive for type 2 diabetes mellitus, brain tumour, Wiskott-Aldrich syndrome and primary immune thrombocytopenia. On physical examination, she was unconscious, hypotensive, with diffuse cutaneous hyperpigmentation and BMI of 17.6 kg/m^2. Initial biochemical investigations showed blood glucose of 0.8 mmol/l, hyponatremia, hyperkalemia, low-normal calcium level (ionized calcium 1.12 mmol/l), hemoglobin A1c of 11.1%. Serum cortisol in daily profile was 19.2.13.3.16.4 nmol/l, ACTH 668.7 pg/ml (7.2–63.3 pg/ml), anti-adrenal antibodies positive at 1 in 160 dilutions. PTH 1,73 pmol/l (1.6–8.6 pmol/l), vitamin D 19.6 nmol/l. Anti-ovarian antibodies 14 U/ml (normal below 10 U/ml). Thyroid hormones and antibodies and were normal; screening for celiac disease negative. The diagnosis of autoimmune adrenal insufficiency was established and the treatment with Hydrocortison initiated, with good clinical response on 3-month follow-up visit. Menstrual cycles are resumed. PTH and calcium values are still low-normal, despite vitamin D supplementation, requiring additional periodical assessment. In a patient with T1DM and a positive family history, further recommendations are needed to alert psysicians about timely serological screening for coexistence of other autoimmune disorders in order to exclude APS.

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Activity of pure, novel and non-steroidal molecules as inhibitors of AK1C enzyme

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Prostate and seminal vesicles are male accessory sex glands secreting fluids that, together with sperm, form the semen. Clear evidence indicating these organs depend on androgens was found the men suffering hypogonadism because, in them, the function of these glands decreases markedly. Because prostate and seminal vesicles are androgen-dependent organs, they have been used as a model to test antiandrogenic drugs in different animal species.
The objective of this study was to demonstrate the antiandrogenic effect of two pure, novel, and non-steroidal molecules (JP01B and JP03) on the hamster's prostate and seminal vesicles.
The biological activity of both compounds was determined as *in vivo* as *in vitro* experiments. The *in vivo* experiments were performed in hamsters castrated and treated with testosterone (T), T, and finasteride/or each one of the new compounds. For the *in vitro* experiments to determine the metabolism of radiolabeled T en the presence or absence of JP01B and JP03, we followed the conversion of T into their radiolabeled metabolites using the human prostate homogenates as a source of steroidal enzymes. The results indicated that JP01B and JP03 significantly decreased the weight of the seminal vesicles but not that of the prostate. However, treatment with T and finasteride (an inhibitor of DHT formation) reduced the mass of both glands. *In vitro* experiments indicated that both new compounds inhibited the activity of the AK1C enzyme by decreasing the formation of labeled 5α-androstane-3β, 17β-diol compared to the control. However, an accumulation of 5α-dihydrotestosterone (DHT) was determined, which also indicates the presence of the enzyme 5α-reductase. It is a well-known fact that DHT increases the weight of the prostate and seminal vesicles. These data could explain that hamsters treated with T and JP01B or T and JP03 did not reduce prostate growth. However, this does not clarify why the seminal vesicles did significantly reduce their weight. One interpretation could be the presence of estrogen receptor β (ERβ) in this tissue, as has been previously demonstrated. The ERβ is capable of inducing mitosis of epithelial cells, cell morphogenesis, and secretory modulation of specific proteins in the seminal vesicles. Therefore, data suggest that JP01B and JP03 could also be ERβ antagonists in seminal vesicles.

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Pituitary and Neuroendocrinology.

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Proliferation index (Ki67) is a powerful predictor of recurrence in pituitary adenoma

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Introduction
In 2017 the term 'Atypical adenoma' was removed from the WHO classification, and 'High-risk adenomas' was introduced as a term to classify those with rapid growth, radiological invasion, and a high Ki-67 proliferation index. In this retrospective cohort study we have sought to identify the clinical and histological characteristics which are associated with worse outcomes.
Methods
Data
We created a dataset of 1793 patients who were discussed at the Pituitary MDT at King's College Hospital, a tertiary centre in central London from the electronic medical record. The nature and date of treatment was recorded as well as clinical characteristics which were hypothesised to be significant. Survival analyses were performed using cox regression, events were recorded as time of re-operation or radiotherapy, patients were censored at time of last follow-up within the electronic patient record. Incidences when radiotherapy or re-operation which occurred less than one year after the initial

treatment were not included within the analysis as these were treated as primary treatment failure rather than recurrence.
Results
Ki67 was strongly associated with recurrence in a multivariate model ($P<0.05$). Hazard ratio 1.08 (95% CE 1.04–1.14). We created risk groups of low (<3%), intermediate (3–9%) and high (<9%) which were also statistically significant ($P<0.05$, (when compared with <3%). Hazard ratios were1.7240 (95% CE 1.1597–2.563) and 2.8109 (1.6804–4.702) respectively. Male sex was also significantly associated with reccurance ($P=0.003$, HR = 1.5873 (1.1648–2.163). The above findings remained the case when only NFPAs were analysed. For non-functioning adenomas, initial presentation with a visual field deficit was a significant hazard for recurrence ($P<0.05$, HR = 1.6300 (1.0740–2.474)). There was no significant increase in hazard between silent corticotroph and other types of non-functioning adenoma.
Discussion
These results demonstrate that the previous 'atypical adenoma' category may be of clinical value. In this cohort Ki67 could be used to stratify patients by risk.

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The expression level and binding affinity of glucocorticoid receptors in patients with Cushing's syndrome

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Summary
Objective
To evaluate the expression level and binding affinity of glucocorticoid receptors (GRs)in patients with endogenous Cushing's syndrome(CS) and to determine whether there is partial glucocorticoid resistance.
Methods
Fifty-eight patients with CS and forty-one age- and sex-matched healthy volunteers were studied. The expression level and binding affinity of GRs in peripheral blood mononuclear cells (PBMLs) were examined by flow cytometry (FCM). The differences between the two groups were compared, and the correlations of GR level and affinity with serum cortisol concentrations and 24-h urinary free cortisol (UFC) were also analyzed.
Results
The expression level and binding affinity of GRs in CS patients were 11.9±2.6 and 5.7±2.0, while the values of normal controls were 21.5±3.4 and 10.7±2.4, respectively. There was a significant decrease in GR expression and binding affinity in the patients with CS. No correlation was observed between serum cortisol concentrations or 24-hour UFC and GR expression or binding affinity in CS patients.
Conclusion
The expression level and binding affinity of GRs are obviously decreased in patients with CS. To overcome glucocorticoid resistance and avoid glucocorticoid withdrawal syndrome after surgical resection of the causal tumor, a higher than physiological dose of glucocorticoid replacement should be given to CS patients after surgery.

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Treatment of acromegalic osteopathy in the real-life clinical practice: The baac (bone active drugs in acromegaly) multicenter study

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Osteopathy is an emerging complication of acromegaly, characterized by increased bone turnover, profound abnormalities in trabecular bone structure and high risk of vertebral fractures (VFs). The therapeutic management of skeletal fragility in acromegaly is a challenge, since the risk of fractures may remain high after the control of acromegaly and the effectiveness of bone-active drugs in this clinical setting is unknown. In this retrospective-multicenter study, we aimed at evaluating the effectiveness of bone-active drugs on risk of VFs in patients with active or controlled acromegaly. Two-hundred-forty-eight patients with acromegaly (114 females; median age 57 years, range 21–88; 137 patients with active acromegaly) were evaluated for prevalent and incident VFs by a quantitative morphometric approach. At the study entry, prevalent VFs were found in 78 patients (31.5%). Treatment with bone-active drugs was performed in 52 patients (21%): oral bisphosphonates in 39 cases, oral raloxifene in 2 cases, oral strontium ranelate in 1 case, i.v. zoledronate in 1 case, s.c. teriparatide in 3 cases, s.c. denosumab in 3 cases, multiple therapies in 3 cases. The median follow-up was 48 months (range: 12–132); for homogeneity, the follow-up was categorized in 1–2 years (48 cases), 2–4 years (84 cases), 4–6 years (93 cases) and >6 years (23 cases). During the follow-up, 65 patients (26.2%) experienced incident VFs in relationship with pre-existing VFs (HR 2.76; C.I. 95% 1.64–4.65; $P<0.001$) and duration of active acromegaly (HR 1.01; C.I. 95%, 1.002–1.02; $P=0.005$), independently of age ($P=0.39$), sex ($P=0.45$), hypogonadism (P-0.99) and diabetes ($P=0.94$). Treatment with bone-active drugs decreased the risk of incident VFs only in patients with active acromegaly at the study entry (HR 0.20, C.I. 95% 0.06–0.68; $P=0.01$), independently of prevalent VFs ($P=0.002$). The effect of bone-active drugs on risk of VFs was not statistically significant in patients with cured/controlled acromegaly (HR 0.61, C.I. 95% 0.26–1.40 $P=0.24$). In conclusion, this multicenter study showed for the first time that bone-active drugs (i.e., most of them with inhibitory effects on bone resorption) may prevent VFs in patients with active acromegaly. Future prospective studies are needed to assess whether anabolic and anti-resorptive bone-active drugs may have different effects in decreasing the risk of VFs in patients with active and controlled acromegaly.

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Macrophages involvement in neuroendocrine tumor behaviour and progression

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Neuroendocrine neoplasms (NENs) are rare tumour showing a wide spectrum of clinical behaviours. Therapeutic options available for NET treatment are rarely curative and mostly palliative, as NETs frequently show resistance to pharmacological therapy. Cancers develop in complex tissue environments, which they depend on. Tumour-associated macrophages (TAMs) are a major cellular component of the tumour microenvironment. Two polarized state of macrophages are described in literature: M1 (anti-tumour promoting effects) and M2 (pro-tumour promoting effects). The role of macrophages

in pancreatic (Pan-) and pulmonary (Lung-) NENs is poorly understood. So, a better understand of the role of macrophages could provide new insights into the behaviour of pulmonary and pancreatic NETs, more effective therapeutics strategies that could overcome pharmacological resistance and provide new immune markers. In NEN TAMs are not well characterized. We aimed to characterized TAM within Pan- and Lung-NEN. Taking advantage of multiparametric flow cytometry analysis we found that the TAMs were, in large part, M2-like. Theyalso express HLADR, CD115, CCR2 and CX-3CR1.To assess the effects of M1, M2 macrophages on biological behaviour of NEN, primary cells and NEN cell lines QGP-1 (pancreatic-NEN) and H727 (pulmonary-NEN) were cultured with macrophages conditioned medium (CM). We found out that CM of M1 macrophages strongly decreased cell proliferation of both Pan- and Lung-NEN primary cells. Effect confirmed in cell lines (QGP-1, H727), where M1 CM significantly decreased tumorigenesis of cells. Interestingly, the CM of NEN cell lines promoted the differentiation of macrophages into an M2 phenotype. A key role in supporting tumours growth is played also by stimuli, such as cytokines. We discovered that QGP-1 and H727 cells secrete specific chemokines and this secretion was influenced by treatment with M1 CM. Sene Set Enrichment Analysis on RNAseq data from QGP-1 and H727 cells treated with M1 CM revealed an enrichment in the genset for inflammatory response, apoptosis and p53 pathway. Results confirmed by mass spectrometry analysis for M1 CM-specific proteins. The supernatant was enriched, compare to control, in complement factors, lysozymes, cathepsin, and hypoxia and stress induction stimuli. A better understanding of the immunological characteristics of the malignancy is necessary to explore and test immunotherapeutic strategies. Using multiparametric flow cytometry technique we decided to perform the immunophenotype of peripheral blood from NEN patients. The present study demonstrated differences of the amount and immunophenotype of circulating granulocytes, lymphocytes, monocytes and their subpopulations between NEN patients and healthy individuals.

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AEP564

Cushing's syndrome & disease: Why does it take so long to diagnose; is the interdisciplinary medical team aware of the signs and symptoms; what are the consequences?

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Background
CS and CD, a baffling portmanteau of symptoms, each often ascribed to other medical conditions, but together representing diagnostically, challenging medical conditions. Often coming, 'disguised', as other stand-alone medical conditions My diagnosis of CS and CD took me on a tortuous diagnostic journey taking almost 6 years to diagnose. My GP, during her 12 years of practice had never diagnosed CS. As part of my current PhD study of CS/CD, one of my objectives is to measure the levels of awareness of these medical conditions by Health Professionals; if they are knowledgeable of the CS/CD signs and symptoms and if they practice effective communication in order to improve their patients' health outcomes.
Work in progress results
A pilot survey was conducted during September 2019 with a study population of 11 Cushing's members of the Pituitary Foundation UK, median age of 47 years. Fifty-five percent of the participants were diagnosed with CS, median length of time for a diagnosis being 2.9 years. Seventy-three percent were diagnosed with CD, median time for diagnosis, 4.3 years, 27% of those were diagnosed with both CS and CD. Forty-five of the participants had to give up work due to their comorbidities created by the disease processes, 21% for psychological reasons and 89% for physical medical conditions. Eighty-two percent were in remission, but all participants were experiencing additional medical conditions which they had not experienced prior to the Cushing's diagnosis. One hundred per cent of the participants reported that they experienced a lack of advice and guidance from their endocrine team, particularly related to family involvement. Only 1 participant had been diagnosed by her GP, the median number of physicians consulted prior to their diagnosis was 4, the median length of time for referral to the endocrine team was 4.5 years. Only 1 participant received advice from their endocrine team about joining a support group. Twelve Health Professionals ranging from GPs, (*2*) Nurses (*3*), medical doctors (*3*), AHPs (*4*) when interviewed had very little or no experience of diagnosing or treating CS or CD.
Conclusion
The interim results suggest that there exists a lack of clinical support and Health Professional awareness of Cushing's which results in an unacceptable length of time for diagnosis. It is crucial therefore that Health Professionals from all disciplines should be made fully aware of the signs and symptoms of CS and CD and the endocrine disorders support organisations.

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AEP565

Hypercortisolism-related molecular signature: Results from whole blood methylome analysis

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The effective treatment and optimal prognosis of hypercortisolism (Cushing's syndrome – CS) depend on accurate and early diagnosis. However, hormonal assays can be complex, requiring multiple tests, and not predictive for any related complications, neither for their duration and severity. Identifying novel, specific and easily measurable biomarkers may improve CS diagnosis as well as the evaluation of complications. Since stress-associated epigenetic markers can be measured at blood level, we analyzed the whole blood methylome of patients, before and after hypercortisolism cure, in order to identify a specific methylation signature of cortisol excess. We collected paired blood samples of 47 patients with confirmed hypercortisolism, obtained before (Pre) and several months after (Post) treatment, and we extracted leucocyte DNA. Methylome data were generated by the Infinium MethylationEPICBeadChip (850K probes; Illumina), and pre-processed and pre-analyzed by adapting different packages (minfi, ChAMP) specifically developed for methylation array analysis for the R software. The entire set of probes was analyzed by both unsupervised and supervised approaches in a training sub-cohort of 48 paired samples (Pre/Post treatment) from 24 patients. The results were then tested on the rest of samples, used as validation cohort. Unsupervised clustering, based on the most variable features, showed a distribution of samples in pairs, each corresponding to an individual, thus expectedly accounting for the highest source of variability among samples. Interestingly, all sample pairs showed a common group of CpGs differentially methylated in the Pre compared to the Post condition, thus indicating the presence of a specific cortisol-related methylation signature. Consistently, the projection of the two most representative components of variability (PCA analysis) allowed to well discriminate Pre samples from Post samples. A supervised pairwise comparison of the samples, performed taking into account some meaningful covariates (particularly blood cell composition), allowed to identify 12 significant CpGs (adjusted P-value < 0.05) perfectly discriminating the Pre from the Post samples. Hierarchical clustering performed on the validation cohort using the same 12 selected CpGs allowed to classify samples according to their status of hypercortisolism with an accuracy of 0.81. The prediction power of the model raised to 0.97 (where 1 corresponds to perfect prediction) when we calculated the C statistic after having performed logistic regression on the validation cohort. Our results show that a specific hypercortisolism-related epigenetic signature exists and that it is measurable at the whole blood level. This approach promises to be powerful to identify specific biomarkers of cortisol excess and of its related complications.

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AEP566

Plasma microRNA levels in patients with active acromegaly

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Background
Plasma microRNAs (miRs) (miR-4446-3p, miR-215-5p, miR-342-5p) were downregulated in patients with active acromegaly (AM) compared with healthy control subjects as assessed by next-generation sequencing.
Aim
The aim of this study wasto validate the previously observed finding in the newly enrolled patients with AM using qRT-PCR.
Materials and methods
Morning plasma samples were collected from fasting patients with AM and age- and sex-matched healthy controls and stored at –80°C. Total RNA isolation:QIAcube with miRNeasy Mini Kit. Reverse transcription was done by TaqMan Advanced miRNA cDNA Synthesis Kit. MicroRNA expression assessed by StepOnePlus Real-Time PCR system with TaqMan Advanced miRNA Assay. We measured plasma expression of five microRNAs: miR-4446-3p, miR-215-5p, miR-342-5p, miR-210-3p and miR-146a-5p. We performed IHC for SSTR2 and SSTR5 expression in tissue samples of patients who underwent neurosurgery. For correlation analysis, we used Kendall rank correlation coefficient.
Results
We enrolled 47 patients with AM – mean age 45.3 years (95% CI 41.5–49.1), body mass index (BMI) 29.9 kg/m^2 (28.3–31.6), gender ratio (m:f) 14:33, IGF-1–710.65 ng/ml (637.84–783.46) and 28 healthy controls matched by age and gender (mean age 44.3 years (39.1–49.5), body mass index (BMI) 27.7 kg/m^2 (25.09–29.45), gender ratio (m:f) 9:19). We found three microRNAs to be downregulated in AM compared with healthy controls. MiR-4446-3p: 0.471 (0.386–0.556) in AM vs 1.023 (0.866–1.180) in healthy controls ($P<0.001$, FDR<0.001). Similarly, miR-215-5p–0.360 (0.263–0.457) in AM vs 0.994 (0.761–1.228) in healthy controls ($P<0.001$, FDR<0.001). Differences in miR-146a-5p levels was 1.201 (1.015–1.387) in AM vs 1.585 (1.272–1.898) in healthy controls ($P=0.036$, FDR$=0.06$). Postoperative adenoma samples were obtained from 42 patients and stained for SSTR2 and SSTR5 expression. Correlation analysis showed positive correlations between GH levels and tumor volume as measured by MRI (0.65, $P<0.001$), SSTR5 expression and tumor volume (0.33, $P<0.05$), miR-210-3p and miR-146a-5p levels (0.28, $P<0.05$); negative correlation between miR-146a-5p and SSTR2 expression (-0.32, $P<0.05$).
Conclusions
In this validation study we confirmed a downregulation of plasma miR-4446-3p, miR-215-5p and miR-146a-5p in patients with AM vs healthy subjects, which makes them promising biomarkers for further research.

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AEP567

Multigene liquid biopsy (NETest) is diagnostic of pancreatic and small bowel neuroendocrine tumours and correlates with imaging

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Introduction
There is a substantial unmet clinical need for an accurate and effective blood biomarker for gastroenteropancreatic neuroendocrine tumours (GEP-NETs). Current monoanalyte biomarkers are ineffective. The NETest, a novel multianalyte signature, provides molecular information relevant to disease biology. We therefore evaluated, under real-world conditions, the clinical utility of the NETest as a liquid biopsy in GEP-NETs.
Aim(s)
Independently evaluate the NETest for diagnosis of GEP-NETs and identification of disease progress in a tertiary referral centre (an ENETS Centre of Excellence).
Materials and methods
Cohorts: pancreatic NETs (PNETs, $n=67$), small bowel NETs (SBNETs, $n=44$) and normal controls ($n=63$). Well-differentiated PNETs, $n=62$, SB-NETs, all ($n=44$). Disease extent assessment at blood draw: morphologic imaging ($n=110$)–CT ($n=106$), MRI ($n=7$) and/or functional 68Ga-DOTA-TATE PET/CT ($n=69$) or 18F-FDG PET/CT ($n=8$). Image-positive disease was defined as either CT/MRI or 68Ga-DOTA-TATE PET/CT/18F-FDG PET/CT-positive. Both CT/MRI and 68Ga-DOTA-TATE PET/CT negative diagnosis in well-differentiated NETs was considered image-negative disease. NETest (normal: 20). Assay: PCR (spotted plates). Data: mean ± S.D.
Results and diagnosis
NETest was significantly elevated in NETs ($n=111$; 26 ± 21) versus controls (8 ± 4, $P<0.0001$). Seventy-five GEP-NETs (42 PNET, 33 SBNET) were image-positive. Eleven (8 PNET, 3 SBNET; all well-differentiated) were image-negative. In image-positive, NETest was significantly higher (36 ± 22) vs image-negative (8 ± 7, $P<0.0001$). NETest accuracy (97%), sensitivity (99%) and specificity (95%). Concordance with imaging: 1) morphologic: NETest was 92% (101/110) concordant with morphologic imaging, 2) functional: 94% (65/69) with 68Ga-DOTA-TATE PET/CT and 3) dual modality (CT/MRI and 68Ga-DOTA-TATE PET/CT): 96% (65/68). In 70 CT/MRI positive, NETest was increased in all (37 ± 22). In 40 CT/MRI negative, NETest was normal (11 ± 10) in 31. In 56 68Ga-DOTA-TATE PET/CT positive, NETest was elevated (36 ± 22) in 55. In 13 68Ga-DOTA-TATE PET/CT negative, NETest was normal (9 ± 8) in ten. Radiological disease status assessment (RECIST 1.1): NETest was significantly higher in progressive (61 ± 26; $n=11$) compared to stable disease (29 ± 14; $n=64$; $P<0.0001$).
Conclusion
NETest is effective as a diagnostic for gastroenteropancreatic NETs. Elevated NETest accurately correlates with diagnosis and identification of disease progress in GEP-NETs.

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AEP568

Modelling neuroendocrine tumours using 3 dimensional cell culturing

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Introduction
In vitro monolayer cell cultures are not able to faithfully model the biological features of the three dimensional (3D) structure of solid tumours. There are limited information about the applicability of 3D cell culturing methods for modeling of tumours of endocrine organs.
Aim
The aim of our work was the establishment and characterization of three-dimensional *in vitro* models of various endocrine tumour cells in order to test their applicability for evaluation of pathomechanisms of tumorigenesis.
Materials and methods
Induction of spheroid formation of tumor cell lines of pituitary (RC4-B/C, GH3), adrenal cortex (H295R) and adrenal medulla (PC12) cell lines were performed using serum-free defined medium (SFDM), ultra-low attachment plate (ULA), hanging drop culturing method and matrigel. AlamarBlue and Trypan Blue assays were used to examine cell proliferation and cell viability. Pharmacological treatment (mitotane, itaconate and glutaminase inhibitor) were applied for studying cell proliferation. Severe combined immundeficient mice (SCID) were used for xenograft formation of H295R cells. *In vitro* and *in vivo* hormone production was assessed by HLPC-MS/MS.3D culture models were compared both to 2D and xenografts models.
Results
While pituitary adenoma cells did not form 3D cultures, *in vitro* spheroid induction of H295R cells were successful by three different methods. PC12 cells (chromaffin cells) formed 3D spheroids using serum-free defined media (SFDM). 3D culturing resulted in changes in cell viability, proliferation compared to 2D monolayer cultures. Interestingly, hormone producing of H295R cells was higher in 3D cultures compared to monolayer cultured cells, similarly to the *in vivo* model.

Conclusion
Based on the phenotype features and biological characteristics (viability, proliferation and hormone production), *in vitro* 3D culture represents a better model of endocrine tumors compared to monolayer culturing. Therapeutic options of neuroendocrine tumours are limited, therefore establishing a new, cheap, easy handling *in vitro* model could help to better understand the pathogenesis and to identify novel therapeutical approaches for these tumors.
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AEP569

Difference in plasma miRNA levels in inferior petrosal sinus samples from patients with ACTH-dependent Cushing's syndrome as assessed by next-generation sequencing (NGS).

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Introduction
ACTH-secreting pituitary adenoma tissue differs from normal pituitary gland tissue in microRNA (miR) expression. MiRs are secreted into circulation and can be detected as potential biomarkers
Aim
To evaluate the difference in miR levels in plasma samples drained from inferior petrosal sinuses in patients with Cushing's disease (CD) and ectopic-ACTH syndrome (EAS).
Materials and methods
we enrolled 24 patients with ACTH-dependent Cushing's syndrome (CS) requiring bilateral inferior petrosal sinus sampling (BIPSS). BIPSS was performed through a percutaneous bilateral approach. Once catheters were properly placed, blood samples were withdrawn simultaneously from each petrosal sinus and a peripheral vein. In addition to ACTH, prolactin measurements were used as additional proof for correct catheter placement. Plasma samples from both sinuses were stored at –80°C. MiRNA isolation from plasma was carried out by an Rneasy Plasma/Serum Kit (Qiagen, Germany) on the automatic QIAcube station according to the manufacturer protocol. To prevent degradation, we added 1 unit of RiboLock Rnase Inhibitor (Thermo Fisher Scientific, USA) per 1 µl of RNA solution. The concentration of total RNA in the aqueous solution was evaluated on a NanoVue Plus spectrophotometer (GE Healthcare, USA).MiR expression was then analyzed by sequencing on Illumina NextSeq 500 (Illumina, USA). The libraries were prepared by the QIAseq miRNA Library Kit following the manufacturer standard protocols. Sequencing was performed on a total of 24 samples. Data analysis and interpretation was conducted on Qiagen GeneGlobe Data Analysis Center.
Results
Among 24 enrolled patients (mean age 48 years (minimum 23, maximum 69); M:6, F:18) 12 subjects were confirmed as CD and 12 as EAS. 108 miRNA were differently detected (P <0,05) in inferior petrosal sinus samples of patients with CD vs EAS. We divided these miRNAs into 3 groups based on the significance of the results. The first group consisted of samples with the highest levels of detected miR in both groups. Four miRNAs were included: hsa-miR-1203 was downregulated in CD vs EAS–36.74 (P=0,013), and three other were upregulated in CD vs EAS: hsa-miR-383-3p 46.36 (P=0,01), hsa-miR-4290 6.84 (P=0,036), hsa-miR-6717-5p 4.49 (P=0,031). The vast majority of differently expressed miRNAs are involved in oncogenesis signaling pathways.
Conclusion
Plasma miR levels differ in inferior petrosal samples taken from patients with CD vs EAS. These miRs need to be validated by different methods and in peripheral plasma samples in order to be used as potentially non-invasive biomarkers to differentiate ACTH-dependent CS.
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AEP570

Challenges in the management of pituitary involvement in granulomatosis with Polyangitis (GPA): 2 cases managed at Imperial college healthcare trust

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Granulomatosis with Polyangitis (GPA) typically affects the lungs, kidneys and ENT system. Pituitary involvement is extremely rare, affecting less than 1% of all cases. The most common pituitary manifestations are secondary hypogonadism and Diabetes Insipidus (DI).Corticosteroids and immunosuppressive agents represent mainstay of medical management. Treatment needs to be initiated promptly and individualised according to clinical response.
Case 1
A 54-year-old woman presented in 2017 with sinusitis, haemoptysis and cavitating lung lesions on imaging. The clinical presentation and strongly positive c-ANCAs and Proteinase 3 (PR3) antibodies led to a diagnosis of GPA. Disease remission was achieved with Corticosteroids, Cyclophosphamide and Mycophenolate (MMF). She re-presented in August 2019 with blurring of vision and headache. Humphrey field testing revealed a bitemporal visual field defect. Secondary hypothyroidism, hypogonadism and DI were confirmed biochemically. A pituitary MRI showed a suprasellar mass with increased peripheral signal enhancement and chiasmal compression. The pituitary/vasculitis MDT felt that the pituitary lesion was likely inflammatory in nature. An increase of prednisolone to 60 mg led to a reduction in the size of the pituitary lesion. She subsequently received two doses of Rituximab together with Cyclophosphamide and the plan is the wean her steroids.
Case 2
A 50-year-old woman presented with haemoptysis and multiple cavitating lung lesions on imaging in 2016. She tested strongly positive for c-ANCA with high PR3 titres. A diagnosis of pulmonary GPA was made. She was started on Prednisolone 60 mg and both Cyclophosphamide and Rituximab. Unfortunately, she developed an allergic reaction to the latter. In 2018, she experienced intermittent headaches. A pituitary MRI revealed an enlarging suprasellar mass with peripheral enhancement, abutting the optic chiasm. Visual fields remained normal. She proceeded to a pituitary biopsy as per the recommendation of the pituitary/vasculitis MDT. This confirmed lymphocytic hypophysitis. She later developed sinusitis and pituitary insipidus confirmed on water deprivation testing. Her most recent pituitary MRI showed an increase in the volume of the pituitary lesion, with a change in its shape suggesting worsening pituitary GPA. PR3 antibody levels were rising. Prednisolone was increased to 60 mg and Azathioprine replaced by MMF. Management of pituitary GPA remains challenging. Both patients developed a pituitary flare whilst their disease had been in remission otherwise. Corticosteroids are important in remission induction, but cause significant morbidity. The response to conventional steroid-sparing agents remains variable and the role for Rituximab in pituitary GPA is to be determined in clinical studies.
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AEP571

Deletion of chromosome 1q24-1q32 and combined pituitary hormone deficiency type 4: Insight into the challenges of genotype-phenotype correlation

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Background
Interstitial deletions of the long arm of chromosome 1 are rare and classified as proximal or intermediate, the intermediate spanning bands 1q24–1q32. This region contains several genes, including LHX4, a LIM-homeodomain transcription factor essential in the early steps of pituitary ontogenesis. Indeed, mutations in the LHX4 gene are related to combined pituitary hormone deficiency type 4 (CPHD4, OMIM 602146).
Aim
outline the impact of a deletion involving the 1q24–1q32 region in two unrelated boys followed in different Italian hospitals (b1: Rome, b2: Milan), enlightening the complex phenotype, including pituitary hormone deficiency.
Case reports
Both boys (b) were born at term, small for gestational age (b1: 2600 gr, –3.6 SDS; b2: 1800 gr –3.3 SDS), from non-consanguineous parents. At birth, common mild dysmorphic features such as very small feet and hands were evident. In both children brain MRI showed a poorly developed sella turcica, pituitary hypoplasia, thin pituitarystalk, ectopicneurohypophysis, and corpus callosum hypoplasia. Nonetheless, hormonal picture was different, showing b1 neonatal hypoglycaemia that led to diagnosis of GH deficiency and central hypoadrenalism, with central hypothyroidism defining the condition of CPHD and having b2 an uneventful neonatal period. In the latter, decreased linear growth was first observed at the age of 6 months. At that time, endocrine evaluation showed normal thyroid function, low GH, IGF-I and cortisol levels, suggesting GH deficiency and central hypoadrenalism. In both patients adequate replacement therapy was started. Due to the complex phenotype, in which CPHD and severe growth retardation were accompanied by mild neurodevelopmental delay, CGH-array was performed. Boys shared a quite similar genotype, with alteration involving the intermediate region of chromosome 1 (b1: del1q25.1q31.3, b2: arr1q24.3q31.1). During follow-up tocurrent age of 5.5 years, auxological and hormonal data were collected. CPHD was confirmed in b1, while in b2 a short synachten test performed at the age of 2 years showed a normal cortisol peak, narrowing the hormonal picture to isolated growth hormone deficiency.
Conclusion
diagnosis of hypopituitarism in neonatal period is extremely challenging. On this context, neuroradiological abnormalities are strongly supportive. Besides, in the era of precision medicine, accurate genotype characterization seems quite essential. However, as these reports show, even though CGH-Array allowed defining a common genetic condition likely causative of the clinical picture, follow-up revealed a different phenotype evolution.

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AEP572

Baseline IGF-I values influence the effect of rhGH therapy on fat mass: Short, medium and long term study on adults with GH deficiency

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Background
One of the main effects of growth hormone therapy (rhGH) in the adult GH deficient patient (AGHD) is to positively modify body composition, with a reduction in fat mass (BF) and an increase in total lean mass (LM). However, the response to replacement therapy is highly variable and, contrary to what described in children, the potential predictive factors are not yet known.
Aim of the study
To assess the impact of basal IGF-I levels on variations of body composition induced by rhGH therapy (median dose 0.2 mg/day) in AGHD.
Study protocol
A monocentric longitudinal prospective study in 44 patients (age at diagnosis 46.1 ± 11 years) with GHD of different aetiology (17 NFPA, 7 craniopharyngiomas, 4 prolactinomas, 4 acromagaly, 2 Cushing diseases, 1 TSH pituitary adenoma, 3 empty sella, 1 Rathke's cleft cysts, 2 hypophysitis, 2 idiopathic, 1 post-traumatic). Patients have been divided into two groups based on theIGF-I basal levels: Group A with IGF-I > –2 SDS (n = 15, 8 M) and group B with IGF < –2 SDS (n = 29, 13 M). Body composition evaluated with dual-energy X-ray absorptiometry and IGF-I levels were assessed at 12 months (n = 44, 21 M), 3–5 years (n = 40, 19 M), and 7–10 years (n = 29, 11 M).
Results
At baseline, no differences were observed between the two groups except for BF %, higher in group B. In the short term, BF % decreased in both groups (from 33 ± 7% to 30 ± 7% group A and from 38 ± 7% to 36 ± 8% in group B, P < 0.05), however, this reduction remained significant in the medium and long term only in group B (35 ± 8% and 37 ± 9%, P = 0.002 and 0.04 vs baseline, respectively). Nevertheless, in both groups, BF% showed an increase at last follow up. Instead, LM showed a sustained increase in both groups and at all times of observation. The IGF-I SDS levels as well as the rhGH dose did not differ between the two groups in the short, medium and long term.
Conclusions
basal IGF-I levels can be predictive of the effect of rhGH therapy on BF %, suggesting greater efficacy in patients with more severe deficiency. The relative increase in BF % observed in the long term still leaves open the question on the parameters to be used in order to define the optimal timing of stopping rhGH therapy in AGHD.

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AEP573

The SAGIT instrument: Potential utility in treatment decision-making in acromegaly

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Introduction
The SAGIT instrument was developed for clinicians to assess the status and evolution of the disease in patients with acromegaly. Currently, it is investigated in the validation phase. The aim of our study was to evaluate the potential utility of SAGIT instrument for distinguishing acromegaly clinical stages and its usefulness in treatment decision-making at a single Polish endocrine center.
Patients and methods
Medical charts of adults with confirmed acromegaly hospitalized at the Department of Endocrinology within the last 24 months were retrospectively reviewed. Clinical and biochemical data were collected. SAGIT instrument was completed using patients' medical records. Patients were divided into three categories: stable/controlled; active/uncontrolled; treatment-naïve. Also, treatment decisions were recorded as: continue current therapy with no change/no treatment initiation; intensify current therapy/initiate a treatment; reduce the current treatment.
Results
Among 108 patients, 58% were female, the average age was 55.5 years, and the median time of disease duration was 90 months. Median BMI was 28.5 kg/m^2. There were 14 treatment-naïve patients. Fifty % (n = 47) of treated patients did not achieve biochemical control. Current acromegaly treatment was continued in 38.3% (n = 18) of these patients. Median SAGIT score in treatment-naïve patients was higher than in treated patients (13 vs 6; P = 0.004). Also, patients who did not exhibit hormonal control had a higher SAGIT score than the controlled group (11 vs 4, P < 0.001). In ROC curve analysis, SAGIT score of 6 or less discriminated controlled patients from uncontrolled (P < 0.0001, sensitivity 85.1%, specificity 77.0%). Lack of signs and symptoms (S = 0) predicted controlled disease with a sensitivity of 83% and specificity of 39.3% (P = 0.0114). In uncontrolled treated patients, SAGIT score higher than seven indicated for treatment change (P = 0.0009, sensitivity 79.3%, specificity 66.7%)
Conclusions
The SAGIT instrument is easy to use even when completed in the retrospective medical-record review. Our study indicates for its potential utility for distinguishing clinical stages of acromegaly and in decision-making.

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Cushing's disease: Assessment of MGMT expression in pituitary corticotroph tumors and its relationship to clinical, pathological and ultrastructural parameters

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Background
O-6-Methylguanine-DNA-methyltransferase (MGMT) is a DNA repair enzyme. It has been demonstrated that its higher expression counteracts cytotoxicity of alkylating agents used in the treatment of glioblastoma or invasive pituitary tumors. Little is known on the relationships between MGMT expression and invasiveness of corticotroph adenomas in Cushing disease (CD).
The Aim
To evaluate MGMT expression and its associations with clinical, neuropathological and ultrastructural features of surgically treated corticotroph tumors.
Study population and methods
This cohort study included 72 consecutive patients (60 females) aged 44.15±15.15 yr operated via transsphenoidal approach (TSS) according to the same surgical protocol. Clinical, pathological and ultrastructural parameters were evaluated in light of surgical outcomes. MGMT expression was graded in four categories (<25%, 25–50%, 50–75%, >75%), Ki-67 labeling index in 3 categories (<3%; 3–10%; and >10% positive nuclei), p53 expression in 3 categories (<5%; 5–50%and >50% possitive cells) and mitotic index (MI) in 2 categories (≤2 vs >2 mitoses per 10 high power fields). Early remission was recognised on the basis of hormonal assessement 6 months after TSS.
Results
The proportions of patients in each MGMT expression category (<25%, 25–50%, 50–75%, >75%) were as follows: 19.4, 15.3, 15.3, 50.0%, respectively. Tumors with lower MGMT expression had significantly larger maximal diameter (medians: 15 mm for <25% vs 6 mm for >75%, P_{trend}=0.001), higher plasma ACTH (medians: 119.45 pg/ml for <25% vs 59.45 pg/ml for >75% MGMT expression, P_{trend}=0.002), higher mitotic index (21.4% patients with MI>2 for <25% MGMT expression vs 2.8% patients with MI>2 mitoses for >75% MGMT expression, P_{trend}=0.026) and higher expression of *P* 53 protein (14.3% patients with *P* 53>50% for <25% MGMT expression vs 0.0% patients with *P* 53 >50% for >75% MGMT expression, P_{trend}=0.007). There was a borderline relationship between higher Ki-67 and lower MGMT expression (P=0.099). We confirmed an association between sparsely granulated ultrastructure of corticotroph adenomas (SGCA) and lower MGMT expression: 64.3% SGCA for <25% vs 22.2% SGCA for >75% MGMT expression category, P_{trend}=0.005). Moreover, men presented with lower MGMT expression (35.7% men in <25% MGMT category vs 2.8% with MGMT expression >75%, P=0.004). Six months after TSS lower MGMT expression predicted lower early remission rate in CD. Early biochemical remission rates in each MGMT categories (<25%, 25–50%, 50–75%, >75%) were: 35.7%, 54.5%, 72.7% and 77.8%, respectively (P=0.036).
Conclusion
The lower MGMT expression is characteristic for more invasive corticotroph tumors that may be associated with a lower effectiveness of surgical treatment of CD.

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Temporal trends in craniopharyngioma management and long term endocrine outcomes

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Background
The management of craniopharyngiomas remains controversial.
Objective
This study sought to examine temporal trends in the management of craniopharyngioma and their impact on long-term patient outcomes, with focus on endocrine consequences.
Methods
This was a cross sectional, multicentre study. Patients treated between 1951 and 2015 were identified and divided into four quartiles based on the date of initial surgery. Patients' demographics, clinical presentation, treatment and outcomes were collected from retrospective medical record review. Temporal trends of the data were assessed during the period of the study.
Results
In total, 142 patients with both childhood onset craniopharyngioma (48/142; 33.8%) and adult onset disease (94/142; 66.1%) were recruited. Quartile one and four contained 36 patients each and quartile 2 and 3 contained 35 patients each. The median follow-up was 15.4 years (IQR 5.4–23.9 years). Variable data were available for the development of deficiency of individual pituitary hormones at latest clinical review. GH was impaired in 88% (119/135; 88%), 81% (99/1121; 81%) were gonadotrophin deficient, 86% (119/139; 86%) had secondary hypothyroidism, and 82% (116/141; 82%) were ACTH deficient. Permanent cranial diabetes insipidus occurred in 63% (87/139; 63%). The incidence of anterior panhypopituitarism reduced significantly across the quartiles during the time course of the study (P=0.004). Anterior panhypopituitarism was not affected by treatment modality (surgery vs both surgery and radiotherapy) (P=0.17). BMI data were available for 105 patients of which 88 (88/105; 84%) had raised BMI with a median BMI of 29.2 kg/m^2 (IQR 25.5–34.6 kg/m^2). There was no association between BMI and the age of diagnosis (P=0.14) and no significant trend of BMI rate over the study period (P=0.14). Across quartiles, there was a significant trend towards using transsphenoidal surgery and away from employing transcranial surgery (P<0.0001). 86 patients (86/138; 62%) received post-operative radiotherapy, the overall use of radiotherapy was not statistically different among the four quartiles (P=0.33). Craniopharyngioma recurred in 51 patients (51/142; 36%). There was no significant difference in the recurrence rate between the two age groups (P=0.4) as well as the rate of recurrence during the time course of the study (P=0.15).
Conclusion
The rate of hypopituitarism in craniopharyngioma has significantly improved reflecting the trend toward less aggressive neurosurgical techniques and high precision radiotherapy. Long term follow is required to provide appropriate care for the complex sequelae in patients with craniopharyngioma.

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AEP576

Sustained response to treatment with oral octreotide capsules: Results from the phase 3, randomized, double blind, placebo-controlled optimal study

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Background
Patients with acromegaly responding to injectable somatostatin receptor ligands (SRL) are often treated for decades without deterioration of biochemical response (except for routine fluctuations in IGF-I control), unless there are changing clinical circumstances such as persistent or recurrent tumor growth. Oral octreotide capsules (OOC) have been formulated as a potential therapy for acromegaly and the safety and efficacy was evaluated in the CHIASMA OPTIMAL pivotal study. In CHIASMA OPTIMAL, 58% of patients receiving OOC met the primary endpoint and maintained their baseline response levels (IGF–I ≤1 ×ULN) vs 19% of patients receiving placebo (P=0.008). At the end of treatment, mean IGF-I levels of the OOC treatment group were maintained within normal range in all patients and 75% of patients in this group maintained IGF-I levels ≤1.1 ×ULN. This analysis describes the durability of OOC treatment response (Samson *et al.* ENDO 2020).

Methods
Patients were ≥18 years of age, had evidence of active disease, and an average IGF-I≤1.0 × ULN receiving a stable dose of SRL injections (≥3 months). Patients were randomized to OOC (40 mg/day; $n=28$) or placebo ($n=28$) for 36 weeks. Dose was titrated to 60 or 80 mg OOC (or placebo) through week 24 at investigator discretion based on increased IGF-I levels and/or worsening acromegaly signs/symptoms. Patients not responding (OOC or placebo) could revert to prior injectable SRL therapy if they met the predefined withdrawal criteria (i.e., IGF–I≥1.3 × ULN for 2 consecutive visits on the highest dose and exacerbation of clinical signs/symptoms). The primary endpoint was proportion of patients maintaining biochemical response, defined as IGF–I≤1.0 × ULN (average: weeks 34 and 36). Patients who discontinued oral treatment (OOC or placebo) were considered non-responders regardless of clinical response at the time of discontinuation (non-response imputation or WOCF). For this analysis, the proportion of week 24 responders (IGF–I≤1.0 ×ULN) in the OOC group who maintained their response at the end of study is presented.
Results
Analyzing a subgroup of 12 patients who were responders (IGF-I≤1.0 × ULN) to OOC when assessed at week 24 (end of dose titration phase) in the OOC treatment arm, 11 of these 12 patients had a sustained or durable response to end of treatment at 9 months (91.7%).
Conclusion
Efficacy was durable in CHIASMA OPTIMAL. This suggests that patients who respond to OOC with maintained normal IGF-I may potentially be maintained on treatment without deterioration in IGF-I control. Longer-term extension studies are ongoing.

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Biochemical control of most patients reverting to injectable long-acting somatostatin receptor ligands is achieved after one dose: Results from the phase 3, randomized, double blind, placebo-controlled optimal study

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Background
Injectable somatostatin receptor ligands (SRLs) are currently the most widely used therapy for acromegaly. Oral octreotide capsules (OOC) are a potential therapy for acromegaly; the safety and efficacy were evaluated in the CHIASMA OPTIMAL pivotal study (Samson *et al.* ENDO 2020). As reported, mean IGF-I levels of the OOC group were maintained within normal range at end of treatment in all patients. However, some patients may not respond to OOC treatment (25% of OOC and 68% of placebo required rescue, $P=0.003$). This analysis describes the degree and rapidity with which patients achieve biochemical control (IGF–I≤1.0 × ULN) when reverted to their prior injectable SRL.
Methods
Patients with confirmed acromegaly and receiving a stable dose of injectable SRL (≥3 months) were randomized to OOC (40 mg/day; $n=28$) or placebo ($n=28$) for 36 weeks. Patients were dose titrated to 60 or 80 mg of OOC (or placebo) through week 24 at investigator discretion based on increased IGF-I levels and/or worsening acromegaly signs/symptoms. Patients could be rescued via prior injectable SRL therapy if they met predefined withdrawal criteria (IGF–I≥1.3 × ULN; 2 consecutive visits on the highest doseand exacerbation of clinical signs/symptoms) or discontinued treatment for any reason. Seven patients in the OOC and 19 in the placebo group required rescue. The change in IGF-I from Baseline was compared to the end of the Double-blind Placebo Controlled period.
Results
In patients rescued up to week 32 (with ≥4 weeks of follow-up), baseline IGF-I levels(mean; Screening Visit 2 and Baseline) were 0.80 and 0.87 × ULN in OOC and placebo groups,respectively. In patients receiving rescue therapy, the end of study IGF-I levels (mean; week 34 and 36) were 0.80 and 0.89 × ULN in OOC and placebo groups, respectively. The median time to return to normal IGF-I values following loss of response was 4.0 weeks after discontinuing either OOC or placebo. Therefore, most patientswho required rescue following a short trial of OOC returned to their baseline values following a single SRL injection.
Conclusion
Most treatment failures in the CHIASMA OPTIMAL trial(either OOC or placebo) rescued with injectable SRL re-established their baseline response levels after a single injectable SRL administration (at pre-study dose). Based on these data, patients may potentially be treated with OOC and for those not responding, either not biochemically-controlled or who have adverse effects, they may be able to return to injectable SRLs with immediate IGF-I control after one SRL injection.

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Association between sagittal spine imbalance and radiological vertebral fractures in acromegaly: Does it reflect a pathophysiological link?

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Chronic exposure to GH hypersecretion may alter the physiological balance of the spine through inducing degeneration of intervertebral discs and impaired trophism of facet joints. Moreover, GH in excess may also cause profound deterioration in bone microstructure with consequent increase in risk of fragility vertebral fractures (VFs). In this cross-sectional study,we evaluated for the first time in acromegaly the association between spine imbalance and VFs. Thirty-eight patients with acromegaly (median age 55 years; 20 males; 12 with active disease) were consecutively evaluated for sagittal spine parameters and morphometric VFs (EOS imaging system, Paris, France), quality of life (SF-36 questionnaire), pain and disability (Womac questionnaire). Thirty-eight subjects without history of pituitary disease, matched for age and sex with acromegalic patients, acted as controls for evaluation of VFs. VFs were significantly more frequent in acromegaly patients as compared to control subjects (34.2% vs 5.3%; $P=0.003$). All fractured patients with acromegaly had VFs in the thoracic tract with spine deformity index (SDI) ranging from 1 to 9. In acromegaly, the prevalence of VFs was significantly higher in patients with kyphosis (i.e., thoracic Cobb angle >50%) as compared to those without kyphosis (55.6% vs 15.0; $P=0.02$). The thoracic Cobb angle in fractured patients was not associated with the SDI ($P=0.61$). In acromegalic patients without VFs, the thoracic Cobb angle was significantly associated with lumbar Cobb angle ($P=0.003$), which in turn was significantly associated with sacral slope ($P<0.001$) and pelvic incidence ($P<0.001$) reflecting compensatory adapation of the spine. These associations were not found in patients with VFs. Acromegaly patients with VFs showed also lower SF-36 Health score ($P=0.002$) and higher Womac-pain score ($P=0.03$) as compared to patients who did not fracture. The association between VFs and SF-36 Health score remained significant ($P=0.005$) after correction for the thoracic Cobb angle, whereas that with the Womac-pain score was lost ($P=0.16$). In conclusion, this study provided a first evidence that: 1) VFs may be associated with spinal kyphosis and sagittal imbalance in acromegaly, likely reflecting an effect ofabnormal spinal compressive loading on fracture risk, such as already demonstrated in post-menopausal osteoporosis; 2) VFs may impact on quality of life of patients with acromegaly, independent of kyphosis; 3) the low dose biplane X-ray imaging system may be proposed in the real-life clinical practice asa reliable diagnostic tool for a comprehensive evaluation of spine arthopathy and VFs in acromegaly.

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Once-weekly somapacitan in japanese adults with growth hormone deficiency was well tolerated, with similar efficacy to daily growth hormone: A randomised trial

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Somapacitan is a long-acting, reversible albumin-binding growth hormone (GH) derivative. The objective of this trial was to evaluate the safety, efficacy and treatment satisfaction of onceweekly somapacitan versus daily GH (Norditropin) over 52 weeks in Japanese patients with adult GH deficiency (AGHD). This was a phase 3, multicentre, randomised, open-label, parallel-group, active-controlled trial (NCT03075644). Patients previously treated with GH were randomised 1:3 to daily GH or somapacitan, to undergo 20 weeks of dose titration and 32 weeks of fixed-dose treatment. The primary endpoint was the incidence of adverse events (AEs) from baseline to week 53. Secondary endpoints included change from baseline in visceral, subcutaneous and total adipose tissue (VAT, SAT and TAT, respectively) assessed with computerised tomography scans; change from baseline in treatment satisfaction, evaluated using Treatment Satisfaction Questionnaire for Medication (TSQM-9) scores; andoccurrence of anti-somapacitan antibodies. In total, 62 patients were randomised (daily GH $n=16$; somapacitan $n=46$); 60 patients completed the trial. Baseline characteristics for daily GH versus somapacitan groups, respectively, were: female, 43.8% vs 47.8%; adult-onset GHD, 87.5% vs 80.4%; mean (S.D.) age, 49.3 (11.5) vs 54.1 (12.1) years; weight 67.9 (12.0) vs 69.4 (22.7) kg; body mass index 24.8 (3.7) vs 26.4 (6.7) kg/m^2; and GH dose at screening 0.29 (0.14) vs 0.31 (0.17) mg. Rate of AEs per 100 patient-years was similar between treatment arms (daily GH, 309.8; once-weekly somapacitan, 312.7). Most AEs were mild (97.9% and 93.1%, respectively); none were severe. Four AEs in the somapacitan arm were serious; all were considered unlikely related to treatment. No anti-somapacitan antibodies were detected during treatment. Mean insulin-like growth factor-I standard deviation score (IGF-I SDS) at baseline was maintained with both treatments. Most patients had IGF-I SDS values <+2. No significant differences in VAT, SAT and TAT were seen in either treatment group after 52 weeks (estimated difference, somapacitan – daily GH [95% CI]): –1.74 [–18.13; 14.66], –11.53 [–35.54; 12.48], and –12.85 [–47.31; 21.62] cm^2, respectively. TSQM-9 scores were not significantly different between treatments, but showed a tendency in favour of somapacitan (estimated difference [95% CI]): 4.87 [–3.46; 13.20] for effectiveness, 6.79 [–1.04; 14.61] for convenience, and 6.88 [–1.08; 14.85] for overall satisfaction. No new safety concerns were identified. Improvements in body composition were similar in both cohorts. The safety and tolerability of somapacitan in Japanese patients with AGHD were consistent with results from the global phase 3 trial (REAL 1).

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AEP580

Real life efficiency of pegvisomant therapy in acromegaly

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Introduction
Pegvisomant (PEG) is an efficient treatment for acromegaly but the recommendation for this treatment is less active due to its high cost. In Romania it is reimbursed in doses up to 30 mg s.c/day or as 40 or 80 mg/week in combination with a somatostatin analog (SSA).
Design
Retrospective analysis of 18 consecutive patients treated with PEG for acromegaly (either as monotherapy, or in combination with SSA and/or cabergoline (CAB), or both consecutively. All patients had a macroadenoma, underwent surgery, all had residual disease, 17 underwent radiotherapy. In the study were included 12 women, 6 men, mean age 44.5 years old (range: 19–70). Before commencing PEG, patients had an elevated IGF◀ level: mean 875.3±397.3 ng/ml. The mean duration of the PEG treatment was 3±1.6 years.
Results
14 patients had PEG in monotherapy, mean dose 16±5.2 mg/day (112 mg/week). From these, 8 normalised IGF1, 2 of them were disease free after RT and PEG therapy. In 4 patients optimal response was not achieved with 30 mg PEG/day. From 6 patients with combined therapy: SSA+PEG or SSA+PEG+CAB (mean PEG dose 58.6±24 mg/week), 2 patients normalised IGF1 (33%). Adding CAB decreased IGF1 levels but did not normalise them. In the whole group 4 patients (22%) had side effects: a tumor increase with 2.5–8 mm in 2 patients, after 8 and 24 months, respectively, and elevated transaminases in 2 patients (1 of these tolerated a lower PEG dose+SSA, the other one stopped PEG therapy).
Conclusions
Pegvisomant is an effective treatment for acromegaly (in 55% in our series), if the dose is well titrated and tolerated during treatment. Special attention is needed for the potential side effects (noted in 22% of our series).

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AEP581

Sheehan like syndrome in males: A case series of three patients developing pituitary infarction following hypotension

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Pituitary apoplexy caused by pure infarction is rare. Here we present three cases of pituitary macroadenoma infarction following hypotension.
1. An 84 year old gentleman had a 2×2 cm pituitary macroadenoma causing chiasmal compression and a bitemporal hemianopia. He had panhypopituitarism and was on prednisolone, thyroxine and testosterone replacement. Before surgical intervention of the macroadenoma, he fell and broke his humerus, which required internal fixation but was complicated by an infected prosthesis. He required further operative interventions. Following a four hours procedure, he reported worsening of vision, which resolved spontaneously. His prolactin which had been 1095 fell to 48 mU/l and a three months interval MRI showed a reduction in size of the pituitary macroadenoma. Pituitary MRI two years later shows only a slender amount of tissue in the sella.
2. A 68-year old man underwent elective coronary artery bypass grafting (CABG). Post operatively he complained ofheadache, blurred vision and had a left sided third nerve palsy. CT head and MRI pituitary confirmed a 3.5 cm pituitary macrodenoma stretching the optic chiasm. Pituitary profile one day following CABG showed TSH 0.89 (NR 0.3–4.2 mU/l), T3 2.7 (2.5–5.7 pmol/l), T4 8.1(NR 9.0–23.0 pmol/l), 3 pm cortisol 125, LH 1.3 (2.0–12.0 u/l), FSH 2.2 (1.7-8.0 u/l), GH 0.17 ng/l, prolactin <13 mU/l. He was started on prednisolone replacement. Because of his recent CABG, timing of neurological surgical intervention was considered carefully. On review in neurosurgery outpatients, a pituitary MRI showed a marked reduction in the size of pituitary adenoma with no compromise of optic chiasm.
3. A 70-year old man with known severe aortic stenosis developed symptoms of a TIA. CT head identified a 1.8 cm pituitary macroadenoma. MRI pituitary showed no chiasmal compromise. Baseline pituitary function showed no deficiency. His cardiac and neurological symptoms with aortic stenosis necessitated urgent valve replacement. He was on cardiopulmonary bypass with BP 60–80 mmHg systolic for one hour during the surgery. He developed secondary hypothyroidism few weeks later. His repeat MRI showed complete involution of the macroadenoma.
Conclusion
Sheehan syndrome is pituitary infarction due to systemic hypotension in physiologically enlarged pituitary. Our patients demonstrate that the same pathophysiology can cause hypopituitarism in males who have a pituitary adenoma rather than pituitary hyperplasia of pregnancy. The location of pituitary gland and its unusual blood supply makes it prone to ischemia in setting of systemic hypotension when physiologically or pathologically enlarged.

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AEP582

An asynchronous double growth hormone secreting pituitary adenoma ofa different proliferative potential – a case report

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Background
Double pituitary adenomas are a rare entity, which requires clinical attention and a careful follow-up.
Case report
A 37-year-old man presented with left-sided painful gynecomastia. He denied typical symptoms of excessive growth hormone (GH) secretion and did not show any acromegalic features. Due to low testosterone and LH levels with mild hyperprolactinaemia, the patient was referred to pituitary MR, which revealed an 11×13 mm right-sided sellar tumor. An increased IGF-1 was noted subsequently (1482 ng/ml; N 109–284 ng/ml), together with the lack of GH suppression in OGTT. Transphenoidal resection of pituitary tumor performed in 2012 led to biochemical (IGF-1 260 ng/ml, GH 0.08 ng/ml) and radiological remission of the disease. A histopathology report revealed a densely granulated somatotropic pituitary adenoma with mild nuclear atypia, expressing somatostatin receptors [sstr2A (+), sstr5 (±)]. Due to gradually increasing IGF-1 levels (with low, although rising, GH values ranging from 0.07 to 0.92 ng/ml) in subsequent years, OGTT was repeated in 2015, showing appropriate GH suppression. In 2016, however, acromegaly recurrence was confirmed both biochemically (increasingly high IGF-1–664 ng/ml – and unsuppressed post-OGTT growth hormone) and in MR imaging. The patient was reoperated in June 2017. The second histopathology reported an oncocytic somatotropic acidophil stem cell pituitary adenoma with Ki-67 > 3% and mitotic figures. Subsequent anterior pituitary lobe insufficiency (adrenal, thyroid and gonadal axis) was found and adequately treated. Complete tumor removal was confirmed by MR performed three months after repeated surgery, as well as a low GH level (0.97 ng/ml), although accompanied by borderline IGF-1 values (277 ng/ml). Eighteen months after surgery, the recurrence of acromegaly was again confirmed, with adenoma regrowth and increased GH (2.31 ng/ml) and IGF-1 (474 ng/ml). Octreotide LAR was started (despite retina wrinkling which was observed when lanreotide was administered before the first surgery), which led to a normalization of GH (0.96 ng/ml) and IGF-1 levels (152 ng/ml), as well as partial pituitary tumor regression after six months therapy.
Conclusion
In a case of GH-secreting pituitary adenoma recurrence after apparent successful surgery, a double pituitary adenoma with more aggressive histology should be considered.

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AEP583

Not just another headache – a rare case of recurrent pituitary collection

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A 27 year old lady presented in 2016 with a 3 month history of intermittent headache and visual disturbance, 3.5 months post-partum. She had a past medical history of cluster headache; treated with verapamil and short courses of oral steroids (she had no recent steroid courses prior to presentation). She was found to have a partial right sixth nerve palsy but normal visual fields on Goldmann's testing. She had biochemical evidence of secondary adrenal insufficiency (sodium 120 mmol/l, random cortisol 31 nmol/l) and hypogonadotrophic hypogonadism (oestradiol <50 pmol/l, LH 3 iU/l, FSH < 1iU/l). She also had polyuria and polydipsia, blood and urine tests were consistent with mild diabetes insipidus. Urgent MRI showed a complex pituitary mass, with suprasellar extension and optic chiasm impingement, thought initially to be a craniopharyngioma. She was commenced on hydrocortisone replacement and desmopressin with good effect. Review of previous MRIs to investigate headaches showed the lesion was not previously present, hence it was unlikely to be a craniopharyngioma. She underwent trans-sphenoidal adenomectomy in November 2016 – unexpectedly, pus was aspirated which was positive for Strep pneumoniae, H. influenzae and Staph epidermidis. Histology showed granulomatous inflammation within a Rathke's cleft cyst. Her adrenal insufficiency and diabetes insipidus resolved post-operatively, but she still had evidence of hypogonadotrophic hypogonadism. Three years following initial presentation, she was re-referred urgently with recurrent polyuria and polydipsia. Reassessment showed central hypothyroidism (TSH 0.19 mU/l, fT4 10.3 pmol/l, ft3 2.7 pmol/l), persistence of hypogonadotrophic hypogonadism (oestradiol <60 pmol/l, LH 6.9 iU/l, FSH 2.5 iU/l) and diabetes insipidus (sodium 145 mmol/l, serum osmolality 294 mmol/kg; urine osmolality 142 mmol/kg). MRI confirmed a recurrence of a loculated pituitary lesion – she underwent further trans-sphenoidal drainage in Oct 2019, but cultures were negative for any pathogens this time.
In addition, she then developed diarrhoea and mouth ulcers, which prompted investigations under the gastroenterology team. Colonoscopy has shown active inflammation within the ileum and colon, and she is being treated for presumed Crohn's disease. Tests for syphilis, blood-borne viruses, sarcoidosis and vasculitis have been negative. Pituitary abscesses are extremely rare (0.2–1% of all pituitary disease) – it is even rarer to have recurrent episodes in the absence of any systemic immunosuppression or pituitary irradiation. Only 8 previous cases of recurrent pituitary abscess have been reported in the literature. Additionally, we discuss whether this patient could have an underlying multi-system condition driving multi-organ inflammation; or whether her pituitary issues could be an extra-intestinal manifestation of inflammatory bowel disease.

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AEP584

A novel mechanism regulating dopamine receptor type 2 (DRD2) signal transduction in PRL- and ACTH-secreting pituitary tumoral cells: The role of cAMP/PKA-induced filamin A (FLNA) phosphorylation in the control of responsiveness to DRD2 agonist

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The actin binding protein filamin A (FLNA) is required for somatostatin receptor 2 (SST2) and dopamine receptor 2 (DRD2) expression, intracellular localization and signaling in GH- and PRL-secreting pituitary tumors, respectively, playing a role in tumor responsiveness to somatostatin analogs and dopaminergic drugs. FLNA functions are tightly regulated by several mechanisms, including FLNA phosphorylation. It has recently been shown that in GH-secreting pituitary tumors FLNA phosphorylation on Ser2152 switches FLNA function from a scaffold that allows SST2 signal transduction, to a signal termination protein that hampers all SST2 antitumoral effects. Aims of the present study were to evaluate in PRL- and ACTH-secreting pituitary tumor cell lines MMQ and AtT-20, endogenously expressing DRD2: 1) the effects of cAMP pathway activation and DRD2 agonist on FLNA phosphorylation; 2) the impact of FLNA phosphorylation on DRD2 intracellular signal transduction.
We found that forskolin increased (+2.87±onefold, $P<0.05$ in MMQ; +1.92±0.8 fold, $P<0.05$ in AtT-20), and DRD2 agonist BIM53097 reduced (–77.3±2%, $P<0.001$ in MMQ; –52.7±3%, $P<0.05$ in AtT-20), FLNA phosphorylation on Ser2152. The overexpression of a phosphomimetic (S2152D) FLNA mutant in both cell lines completely prevented DRD2 antiproliferative effects, that were comparable in cells transfected with empty vector, wild type FLNA as well as phosphodeficient FLNA mutant (S2152A) (–20.6±5%, $P<0.001$ in MMQ; –36.6±12%, $P<0.01$ in AtT-20). Accordingly, S2152D FLNA expression abolished the expected ability of BIM53097 to increase (in MMQ) or decrease (in AtT20) ERK phosphorylation, an effect that was maintained in S2152A FLNA expressing cells (+178±65%, $P<0.05$ in MMQ; –55±13%, $P<0.01$ in AtT-20).
In addition, the inhibitory effects of DRD2 on PRL secretion (–19±1%, $P<0.05$ in MMQ expressing S2152A FLNA) were completely lost in S2152D FLNA transfected cells. In conclusion, our data demonstrated that cAMP pathway and DRD2 agonist regulated FLNA activity by increasing or decreasing, respectively, FLNA phosphorylation on Ser2152. Moreover, we found that FLNA phosphorylation prevented DRD2 signaling in PRL- and ACTH-secreting tumoral pituitary cell lines, suggesting that this post-translational FLNA modification might represent a new GPCRs regulatory mechanism. In pituitary tumors expressing DRD2, modulation of P-FLNA

might suggest new pharmacological strategies to overcome drug resistance, and P-FLNA might represent a new biomarker for tumor responsiveness to dopaminergic drugs.

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AEP585

Kisspeptin-54 accurately identifies hypothalamic dysfunction in men with congenital hypogonadotropic hypogonadism

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Background
Hypogonadotrophic hypogonadism is characterised by hypogonadism in the context of low/inappropriately normal gonadotrophin levels. Congenital Hypogonadotrophic Hypogonadism (CHH) occurs due to disrupted GnRH neuronal migration, or impaired hypothalamic GnRH secretion or action. However, no direct test of hypothalamic GnRH neuronal function currently exists. Kisspeptin-54 is a neuropeptide that stimulates endogenous hypothalamic GnRH release. Thus, we investigated whether kisspeptin-54 could be used to interrogate hypothalamic function in men with CHH.
Methods
Men with CHH (low testosterone, low/inappropriately normal gonadotrophin levels, incomplete pubertal development; $n=21$) and healthy eugonadal men ($n=21$) received an intravenous bolus of either GnRH (100 mg), or kisspeptin-54 (6.4 nmol/kg), on two study visits at least one week apart. Serum gonadotrophins were measured every 15 mins for 6 hrs following injection. Increases in serum gonadotrophins from baseline following GnRH/kisspeptin in eugonadal men and CHH were compared by Mann Whitney U test.
Results
The maximal rise in LH following KP54 was significantly greater in healthy men (12.5 iU/l) than in men with CHH (0.4 iU/l; $P<0.0001$). Following KP54, all men with CHH had an LH-rise <2 iU/l, whereas all healthy men had an LH-rise >4 iU/l. Thus, the LH-rise after KP54 more effectively discriminated men with CHH from healthy men (auROC 1.0) than GnRH (auROC 0.88). Anosmic men with CHH (ie Kallmann syndrome) had even lower LH-rises following KP54 than normosmic men with CHH ($P=0.017$).
Conclusion
In summary, akisspeptin-54 test of hypothalamic GnRH neuronal function more accurately discriminated men with CHH from healthy men thana GnRH test. Consequently, a kisspeptin-54 test can be used to better identify patients with CHH to direct genetic testing, and to rapidly assess for evidence of spontaneous reversal of hypothalamic dysfunction in patients with known CHH. Thus, KP54 demonstrates potential as a specific test of hypothalamic GnRH function when assessing patients presenting with disorders of puberty.

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AEP586

Growth hormone-releasing hormone (GHRH) promotes survival and proliferation of neural stem cells and reduces amyloid-β-induced toxicity

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Neurogenesis, a process by which new neurons are generated from precursors, still persists in discrete regions of the adult hippocampus. Impairment in neurogenesis is an important feature in the pathogenesis of neurodegenerative diseases, such asAlzheimer's disease (AD). The hippocampus is critical for learning and memory and is a main target of AD, which causes massive neuronal death, reduction in neurogenesis and impairment in cognitive functions. Therefore, preventing neuronal loss or increasing the production of new neurons may represent a potential therapeutic strategy to reduce AD-induced cognitive decline. Growth hormone-releasing hormone (GHRH), apart from promoting growth hormone (GH) secretion from the pituitary, exerts many extrapituitary functions, including stimulation of cell survival, cardioprotection and protection against diabetic retinopathy. Furthermore, expression of GHRH, as well as GHRH-receptor (GHRH-R) and its splice variants (SVs), has been demonstrated in different brain regions, including the cerebral cortex, cerebellum and brain stem cells. To date, however, the role of GHRH on neurogenesis and neuroprotection is still unknown. Thus, we sought to investigate the role of GHRH on survival, proliferation, apoptosis and differentiation of rat hippocampal neural stem cells (NSCs), in stress conditions such as growth factor deprivation and amyloid-β peptide 1–42 ($A\beta_{1-42}$)-induced toxicity, and to define the underlying mechanisms. We found expression of both mRNA and protein for pituitary GHRH-R in NSCs. Moreover, GHRH dose-dependently increased cell survival and proliferation and reduced apoptosis in NSCs culturedunder both growth factor deprivation and $A\beta_{1-42}$. In addition, GHRH counteracted the effect of $A\beta_{1-42}$on elevation of the proapoptotic protein BAX and inhibition of the antiapoptotic protein Bcl-2. Finally, the role of GHRH was examined on differentiation of NSCs into neuronal lineages, such as neurons, oligodendrocytes, and astrocytes. Interestingly, GHRH increased the mRNA levels of the neuronal marker *Tuj1*, while showing no significant effect on *GFAP* and *Ripk1*, specific for astrocytes and oligodendrocytes, respectively. Collectively, these results, suggest a role for GHRH in preventing neuronal loss and in promoting neurogenesis, with potential therapeutic application of its agonistic analogs in neurodegenerative diseases, such as AD.

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AEP587

Pancreatic neuroendocrine tumour with suspected extrarenal secretion of 1,25-dihydroxyvitamin D3

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Background
Hypercalcaemia can occur in 20–30% of malignancy. Neuroendocrine malignancy-related hypercalcaemia is relatively rare with few reported cases, mostly in pancreatic neuroendocrine tumours. It could be related to humoral hypercalcaemia of malignancy (PTHrP secretion), production of 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D3$) by the tumour or production of PTH by the tumour[1,2]. Here we describe a case of metastatic neuroendocrine tumour with possible extrarenal secretion of $1,25(OH)_2D3$, which to our knowledge was previously described in one other case report[3].
Clinical case
A 44-year old gentleman had presented with symptoms of tiredness and vague abdominal discomfort for 3 months. Initial tests showed moderate hypercalcaemia with adjusted calcium of 3.28 mmol/l (2.20–2.60 mmol/l). There was mild hypophosphataemia of 0.58 mmol/l (0.80–1.50 mmol/l) suggestive of a PTH-related effect. However, serum PTH was suppressed at 0.2 pmol/l (1.3–9.3 pmol/l). Serum total 25-OH Vitamin D was within reference range at 31.9 nmol/l (25–50 nmol/l) but surprisingly $1,25(OH)_2D3$ level was elevated at 142 pmol/l (20–120 pmol/l). PTH-related peptide measurement was not performed due to resource limitations. Urinary calcium:creatinine ratio was 2.00 and urinary calcium excretion was high at 25.3 mmol/24 hours (2.5–7.5 mmol/24 hours) which excluded familial hypocalciuric hypercalcaemia. Serum and urine protein electrophoresis were negative for monoclonal band (paraprotein). CT abdomen demonstrated a large 14 cm retroperitoneal partly enhancing solid and partly cystic/non-enhancing mass in the upper abdomen suspected to be arising from the tail of the pancreas. There was a similar lesion in the right lobe of his liver which was hyperenhancing measuring 8.5 cm, and splenic vein obstruction with numerous collaterals. Ultrasound guided biopsy of his liver lesion showed features of neuroendocrine tumour with strongly positive immunohistochemistry stain for AE1/AE3 and Synaptophysin and weakly positive with Chromogranin and focal positivity with S100. The tumour was negative with PAX-8, Melan-A, SMA, Calretinin, CD31 and Desmin. Ki-67 index was 37.1% indicating a high-grade neuroendocrine tumour.
Hypercalcaemia was acutely managed by intravenous hydration and Zoledronic acid. As the tumour was high-grade with metastases, a decision was made for 3-weekly chemotherapy with Carboplatin and Etoposide, with serial CT monitoring.

Conclusion
Neuroendocrine malignancy should be considered as a potential cause of hypercalcaemia in malignancy. This case illustrates a pancreatic neuroendocrine tumour with possible extrarenal secretion of $1,25(OH)_2D3$ level resulting in hypercalcaemia.

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AEP588

New advances in the diagnosis of gonadotroph tumours

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Introduction
Gonadotroph tumours (GT) are the most common subtype of silent pituitary neuroendocrine tumours. The diagnosis of this subtype of tumours is established after surgery. There are no reliable markers of aggressiveness to predict their clinical course and, moreover, immunohistochemistry (IHC) usually classifies GT as null cell tumours. The aim of the present study was to correlate molecular, immunohistochemical and biochemical gonadotropin expression, to quantify the gene expression of transcription factors of gonadotroph lineage and to correlate molecular data with demographic, clinical and radiological variables.
Material and methods
34 molecularly identified GT were selected from PitNET collection of the Biobank of the Alicante Health and Biomedical Research Institute. Demographic variables (age, gender), clinical variables (neurophthalmological manifestations, pituitary hormone deficiency, invasiveness of the cavernous sinus, maximum tumour diameter, re-intervention), biochemical variables (pre-surgical concentrations of FSH and LH), IHC variables (protein expression of FSH and LH) and molecular variables (expression of FSH, LH, gonadotroph lineage transcription factors (ESR1, SF1 and GATA2)) were studied.
Results
13 patients (38.2%) were women and 21 (61.8%) men. The average age was 58.9±15.4 years. Among neurophthalmological manifestations the most prevalent was the oculomotor manifestation (58.8%) followed by headache (38.2%). 24 tumours (70.6%) were invasive. GT showed higher expression of GATA2 gene (mean: 10.590±9.309) compared with SF1 (mean: 0.619±0.284) and ESR1 (mean: 0.225±0.271). We observed a statistically significant correlation between gene and IHC expression of FSH ($r=0.380$, $P=0.024$). Protein expression of FSH correlated positively with pre-surgical concentrations of FSH ($r=0.45$, $P<0.01$). Tumour size correlated negatively with FSH gene expression ($r=-0.44$), $P<0.01$). None of the aforementioned variables had a significant association with growth and aggressiveness ($P>0.05$).
Conclusions
The positive correlation between pre-surgical levels of FSH and the IHC expression of FSH would allow anticipate the diagnosis of GT before surgery. The quantification of expression gonadotroph-lineage transcription factor genes could help diagnose these tumours.

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AEP589

The cushing's collaborative patient survey results

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Background
Early diagnosis of Cushing's syndrome and initiation of effective treatment are essential to limit long-term morbidity and early mortality. However, diagnosis is often delayed due to the non-specificity of symptoms, or because symptoms are not recognised by physicians, leading to more complex treatment needs and a worsening of patient quality of life. A survey was conducted to better understand the patient experience of Cushing's syndrome and the true burden of the disease. Here we report preliminary results from an interim analysis.
Method
An 11-question online patient survey, available in English and translated to eight languages, was distributed via the World Alliance of Pituitary Organisations and local patient organisations. All survey feedback received between 19 March 2019 and 19 January 2020 was analysed.
Results
In total, 250 participants from 26 countries participated; 58% of participants were aged 35–54 years and 92% were female. After diagnosis and subsequent treatment, 37% of participants surveyed reported that they were not satisfied with their treatment. The five symptoms reported most burdensome were obesity/weight gain (15.5%), fatigue (10.7%), depression/mood problems (9.5%), sleep disturbances (8.7%) and anxiety (8.2%). A delay in diagnosis of more than 2 years was reported in almost half of survey participants and a delay of more than 3 years was reported in 27% of participants. Endocrinologists (62.4%), followed by primary care physicians (16.0%), most commonly made the initial diagnosis or prescribed screening tests for Cushing's syndrome Endocrinologists (98%) and primary care physicians (53%) were also most commonly involved in disease management after diagnosis. After treatment, 83% of participants still experienced symptoms of Cushing's syndrome, including fatigue (72.0%), muscle weakness (47.0%), obesity/weight gain (43.1%), memory problems (41.4%) and lack of attention/concentration (38.8%). Despite the ongoing nature of these symptoms, many patients reported not receiving treatment for them. The symptoms most commonly treated were depression/mood problems and anxiety (40.5%), hypertension (36.0%), bone problems and fragility (23.9%), sleep disturbances (17.0%) and muscle weakness (12.1%). Most participants said that their work and social life had been most affected by their illness.
Conclusion
Results from this survey suggest that many patients experience a delayed diagnosis and that even after diagnosis and treatment, patients can continue to experience symptoms that affect their work and social life, and the disease burden post treatment remains high. Correct and timely diagnosis, as well as management strategies that address the wider symptoms of the disease, may improve the patient experience.

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AEP590

High-dose corticosteroid treatment of immunotherapy-induced hypophysitis: A multi-centric, restrospective analysis

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Introduction
Hypophysitis is a frequent side effect of oncologic immunotherapy. The recommended standard treatment is systemic high-dose corticosteroids (HDS), however, recent studies have questioned the benefits of this treatment. We sought to examine the effect of HDS on immunotherapy-induced hypophysitis (IH) in a multi-centric cohort.
Methods
Medical records of 41 patients with IH treated by specialist endocrinologists at three tertiary referral centres in Germany and the UK were retrospectively analysed. Only patients with a follow-up of ≥6 months were included (mean 25±14 months). While 29 patients did not receive specific treatment of IH, 12 were treated with HDS. Pituitary function, symptoms and MRI signs of IH during the course of disease were encoded into a database. We compared the groups using chi square test with a significance threshold of 0.05.

Results
The most frequently used drug for HDS was prednisolone ($n=10$, 40–80 mg/day), the other two patients received dexamethasone. Pituitary function improved (i.e. at least one hormone axis recovered) more often after HDS (5/12) than w/o treatment (6/29), however, the level of significance was not met ($P=0.16$). On the other hand, symptoms (mostly fatigue) resolved more often under hormonal substitution in untreated patients (15/29 vs 4/12; $P=0.28$). An improvement of MRI findings was observed in a similar portion of patients in both groups (25% HDS; 24% w/o treatment; $P=0.95$). Overall, none of the differences in outcomes reached the level of significance.
Conclusions
In our cohort, the course of IH did not differ significantly in patients with and w/o HDS. This finding aligns with other studies that could not find benefits of HDS. Instead, an appropriate replacement of hormone deficiencies seems sufficient.

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AEP591

Assessment of hypercoagulability in patients with cushing syndrome before and after surgical cure

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Background
Patients with Cushing's Syndrome (CS) have a high risk of venous thromboembolism (VTE) related to a hypercoagulable state. Previous studies showed increased levels of procoagulant factors but also an elevation of some of the anticoagulants factors and fibrinolytic enzymes. Once patients achieve disease remission, there is a significant decrease of some procoagulant factors but if these alterations are completely reversible is still unclear. Compared to traditional tests, thrombin generation assay (TGA) provides a global representation of haemostasis. Previous studies with TGA demonstrated that patients with endogenous hypercortisolism present a hypercoagulable profile compared to healthy controls.
Aim
To assess the short- and long-term modification of TGA in patients with CS after disease remission.
Patients and methods
19 patients with CS (16 pituitary adenomas, 2 adrenal adenomas, and 1 ectopic CS, female/male: 12/7, mean age 44.8±11,4 years) that achieved surgical remission and 19 controls matched for age and gender. Clinical characteristics, cortisol secretion profile and TGA parameters before surgical intervention, after 6 months and 5 years of persistent remission were assessed. Endogenous thrombin potential (ETP) ratio (ETP with/ETP without thrombomodulin) represents the resistance to the anticoagulant activity of the thrombomodulin and may be considered the best parameter through which in vivosubtle procoagulant imbalance can be detected.
Results
– Cortisol secretion profile: morning serum cortisol levels: 20.3 (median, IQR: 17–29) µg/dl, serum cortisol after 1 mg DXM: 12.7 (IQR: 4.2–17) µg/dl, urinary free cortisol: 1.65×ULN (IQR: 0.9–2.6)
– TGA: Patients with CS showed an ETP ratio significantly increased compared to controls (0.62±0.09 vs 0.56±0.09; $P=0.034$). No significant correlation between ETP ratio and cortisol secretion was found.
6 months after remission
– TGA: CS patients presented an ETP ratio significantly increased compared to controls (0.64±0.09 vs 0.56±0.09, $P=0.01$) and similar to baseline (0.64±0.09 vs 0.62±0.09, $P=0.87$).
5 years after remission
– TGA: ETP ratio of CS patients showed a significant decrease (0.55±0.14 vs 0.62±0.09, $P=0.02$) and was similar to the controls (0.55±0.14 vs 0.56±0.09, $P=0.7$).
Before surgery:
Conclusions
Plasma hypercoagulability detected in patients with active hypercortisolism persists at short-term and seems to be reversible after long-term remission of disease. Our observation is in line with other studies that demonstrated an increased VTE risk in post-operative period and suggests that in CS patients, especially in the presence of other risk factors for VTE, a long-term antithrombotic prophylaxis should be considered.

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AEP592

Morphometric vertebral fractures are highly prevalent in patients with non-functioning pituitary adenoma and related to older age and hypopituitarism

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Introduction
Recent studies showed that morphometric vertebral fractures (VF) are an early and frequent complication in patients (pts) withhyperfunctioning pituitary adenomas and hypopituitarism (independently from the etiology). GH excess or severe deficiency play a negative key role on bone health in this clinical setting. Disease control or adequate replacement therapies still remain a cornerstone for the clinician to reduce the burden of osteo-metabolic complications. To date, however, data on skeletal outcomes in pts with non-functioning pituitary adenomas (NFPA) are scanty.
Purpose of the study
To retrospectively evaluate the prevalence and determinants of VF in pts with NFPA.
Patients and methods
We consecutively enrolled 98 pts [51 males (M), 47 females (F); mean age 53±12 years old] with NFPA, attending the Pituitary Unit in IRCCS Ospedale San Raffaele for trans-sphenoidal surgery (TNS). We collected all biochemical data on pituitary function and histological exams. Pituitary hormonal deficiency was defined in case of low peripheral hormone levels and inappropriately normal or low pituitary hormones or in all those cases when replacement therapy was already prescribed. Consequently, hypopituitarism was defined by the presence of at least one pituitary deficiency. The vertebral fracture assessment (VFA) was based on Genant classification and completed on chest X-ray (MTRx), performed for anesthesiologic reasons.
Results
We observed a high prevalence of VF in pts with NFPA: 27 out of 98 pts (27.5%) were fractured and 10 (37.04%) had multiple VF, with no gender differences (M17/F10; *P=0.18*). Fractured pts were significantly older than non-fractured ones (mean age 57.93±12.52 vs 51.83±11.94; *P=0.03*). Moreover, pts with VF had significantly lower levels of fT3 (mean 2.26±0.71 vs 2.71±0.55 pg/ml; *P=0.005*) and GH (mean 0.39±0.53 vs 0.85±1.72 mg/ml; *P=0.05*). Based on biochemical parameters of pituitary axes, 56 pts (57.14%) had hypopituitarism. The prevalence of VF was significantly higher in pts with hypopituitarism: 20 out of 56 pts showed VF (35.7%) as compared to those without hypopituitarism (7/42, 16.67%) (*P=0.04*). Finally, the histological examination was positive for FSH in a significantly higher number of pts with VF than in non-fractured ones (15/27, 55.56% vs 23/71, 32.39%; *P=0.04*).
Conclusions
Our data demonstrated a high prevalence of VF in pts with NFPA. Based on these results, we suggest to perform a VFA in pts with NFPA at diagnosis, particularly those with hypopituitarism. Prospective post-surgical studies are needed to evaluate the incidence of VF and its relationship to biochemical and histological parametrs as well as surgical outcomes.

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AEP593

Course of serum potassium levels during the hypertonic saline infusion test for diagnosis of diabetes insipidus

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Introduction
Onset of hyperkalemia has previously been reported during the administration of hypertonic resuscitation solutions. Since the hypertonic saline infusion test has recently been validated for the diagnosis of diabetes insipidus, we aimed to investigate the course of plasma potassium levels during the test.
Material and methods
Data of 144 patients undergoing osmotic stimulation with hypertonic saline infusion at 11 tertiary medical centres in Germany, Switzerland and Brazil from July 2013 to June 2017 were analyzed. Patients received a 250 ml bolus of 3% NaCl solution, followed by 0.15 ml/min/kg body weight continuously infused targeting a plasma sodium level of 150 mmol/l. Blood samples and clinical data were collected every 30 minutes. The primary outcome of this secondary analysis was percentage of patients developing hyperkalemia.
Results
Of the 144 patients, 9.7% (n =14) developed hyperkalemia of >5 mmol/l, 2% (n=3) >5.5 mmol/l and 0.7% (n=1)>6 mmol/l. The majority of the affected patients were diagnosed with primary polydipsia (86% >5 mmol/l and 100% in the other 2 groups). Hyperkalemia was transient and not clinical symptomatic in all patients. Onset of hyperkalemia was related with duration of the infusion test, showing a peak after 120 minutes. A plasma sodium <146 mmol/l at 30-minute test duration was associated with development of hyperkalemia >5 mmol/l (OR 5.5, 95% CI 1.6–25.4, P=0.01). No association was found with plasma chloride or pH levels.
Conclusion
Patients with primary polydipsia are at risk to develop hyperkalemia while undergoing hypertonic saline infusion test, although its incidence is low. Particular attention should be paid if test duration exceeds 90-minutes and in patients with a plasma sodium <146 mmol/l after 30 minutes.

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AEP594

Concordant testing results in differential diagnosis in ACTH-dependent cushing's syndrome: A retrospective study of high dose dexamethasone suppression test (HDDST) and DDAVP stimulation test

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Background
Investigating the origin of ACTH determine disparate treatment and prognosis in ACTH-dependent Cushing's Syndrome. We want to detect the value of combination of HDDST and DDAVP stimulation test for identifying Cushing's disease (CD) and Ectopic ACTH-dependent Cushing's Syndrome (EAS).
Methods
We retrospectively recorded 102 ACTH-dependent Cushing's Syndrome (87 CD and 15 EAS) in West China Hospital from January 1, 2010 to December 31, 2019. Focus on HDDST and DDAVP test, evaluated sensitivity (SE), specificity (SP) and cut-off obtained with ROC analysis respectively, estimate diagnostic accuracy when experiencing concordant tests.
Results
EAS patients have higher ACTH, serum cortisol, 24 h UFC levels, inversely weaker response to 1 mg dexamethasone suppression test (1 mg-DST) than CD (P<0.01). As for HDDST, 24 hUFC suppression below 61.69% suggested a pituitary origin with a SE of 81% (95% CI : 70–90) and a SP of 79% (95% CI : 49–95). Suppressed series had lower baseline level compared with non-suppressed group (P<0.01). A threshold percentage ACTH increase after DDAVP stimulation of 44.63% was able to identify CD with a SE of 91% (95% CI 83–97) and a SP of 80% (95% CI 52–96). When two parallel test results consistent, the diagnostic accuracy matched to BIPSS or pathology verification could reach 95.52%, up to 100% attached MRI≥6 mm findings.
Conclusion
Combined with HDDST and DDAVP stimulation test can enhance accuracy rate searching origin of ACTH secretion, especially in cases with≥6 mm MRI uncovering, BIPSS could be avoid.

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AEP595

Gallium-68 -DOTATATE PET imaging in clinically non-functioning pituitary macroadenomas

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Background
Clinically non-functioning pituitary macroadenomas (NFMA) have been reported to express various somatostatin receptor (SSTR) subtypes, but results are inconsistent across different studies. This may be related to limited sensitivity and specificity of techniques used to date, i.e. immunohistochemistry in surgical specimens and ^{111}In-DTPA-octreotide scintigraphy (Octreoscan) *in vivo*. The aim of this study was to assess SSTR expression in NFMA *in vivo* using ^{68}Ga-DOTATATE PET, which provides superb $SSTR_2$affinity and offers superior sensitivity and spatial resolution as compared to Octreoscan. An additional interest was the proportion of patients with a T2-hypointense adenoma on MRI and the relation with tracer uptake, as T2-hypointensity has been associated with higher $SSTR_2$expression in GH-secreting adenomas.
Methods
Forty-nine patients diagnosed with NFMA underwent ^{68}Ga-DOTATATE PET/CT of the head in the framework of a randomised controlled trial assessing the effect of the somatostatin analogue lanreotide on NFMA size. ^{68}Ga-DOTATATE uptake was assessed after co-registration with T1-weighted pituitary MRI. A circular region of interest was placed within the adenoma and the mean standard uptake value (SUV_{mean}) was evaluated. An SUV_{mean} of >2 was considered positive. Signal intensity of the adenoma was assessed visually on a coronal T2-weighted sequence of the same MRI and was classified as hypointense, isointense or hyperintense as compared to normal pituitary tissue.
Results
^{68}Ga-DOTATATE uptake was positive in 45/49 patients (92%), with SUV_{mean} in positive adenomas ranging from 2.1 to 14.4 (median 5.5). A T2-hypointense, -isointense, and -hyperintense adenoma was observed in 2 (4%), 13 (37%), and 33 (69%) patients, respectively. In one patient T2-signal intensity was not assessed due to a predominant cystic adenoma. SUV_{mean} was not associated with maximum NFMA size or with T2-hypointensity.
Conclusions
This first series of ^{68}Ga-DOTATATE PET performed in NFMA patients demonstrates *in vivo* SSTR expression in the vast majority of cases. The high positive uptake rate when compared to earlier results obtained using Octreoscan (92% vs ~66%) most probably reflects the superior sensitivity and higher spatial resolution of PET imaging. Only 2 patients had a T2-hypointense adenoma, which did not coincide with high tracer uptake. It thus remains uncertain whether T2-hypointensity reflects $SSTR_2$ expression. The clinical use of ^{68}Ga-DOTATATE PET in selecting NFMA patients for somatostatin analogue treatment should be evaluated in well-designed intervention trials.

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AEP596

Efficacy and safety of long-acting pasireotide (LA-PAS) in patients with uncontrolled acromegaly: Results from the prospective cohort of european observational acronis study

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Introduction
Results of the first European real-world evidence from retrospective cohort of ACRONIS study previously confirmed the efficacy and tolerability of LA-PAS in heavily pre-treated, uncontrolled acromegaly patients. Here, we report results of the second interim analysis reflecting the prospective cohort.
Methods
Patients who were treated with LA-PAS for ≥6 months were included in this analysis. The primary objective was to document treatment efficacy, defined by the proportion of patients who achieved IGF-1 level normalization <1 upper limit of normal (ULN) and GH <1 µg/l at 6 months of LA-PAS treatment. Key secondary objectives were changes from baseline in standardized IGF-1 and GH levels, proportion of patients with IGF-1 normalization and GH normalization over time, overall safety and tolerability of LA-PAS.
Results
On 13 Sep 2019, 112 of 200 enrolled patients completed 6 months LA-PAS treatment. Among these, 94 and 109 were included in efficacy and safety analysis, respectively. The mean age of the patients was 50.1 years; 51.1% were male. Median time since diagnosis was 66.5 months; 73.4% had previous surgery and 19.1% had radiotherapy; 98.9% had taken prior medication, mainly first-generation SSAs (58.5% octreotide, 61.7% lanreotide), growth hormone receptor antagonists (38.3%) or dopamine agonists (37.2%) as mono- or combination therapy. In the safety analysis set, 22.0% and 37.6% of patients were diabetic or pre-diabetic prior to LA-PAS prescription, respectively. IGF-1 normalization <1 ULN and random GH <1 µg/l was achieved in 31.9% (95% CI, 21.4–43.9) of patients and IGF-1 normalization <1 ULN and random GH <2.5 µg/l in 44.4% (95% CI, 32.7–56.6) at 6 months. Median (95% CI) percentage reductions from baseline in IGF-1 and GH were 34.3% (43.0–27.6) and 66.8% (73.4–52.9) at 6 months, respectively. IGF-1 normalization (<1 µg/l and <1.3 µg/l) was achieved in 51.8% (40.6–62.9) and 72.3% (61.4–81.6) at 6 months. After median exposure of 22.1 months (range 5.9–29.8), 68.8% remained on starting dose, 22% were up-titrated once, 4.6% were down-titrated once and 4.6% required multiple dose changes. The most common adverse events (AEs in >10%) reported were hyperglycemia (21.1%), diagnosed diabetes mellitus (12.8%) and diarrhea (10.1%). One patient reported permanent discontinuation of LA-PAS due to Grade 2 hyperglycemia.
Conclusion
Findings from this prospective ACRONIS dataset confirm the efficacy of LA-PAS in previously uncontrolled acromegaly patients and are in agreement with those reported in a previous randomized trial (Gadelha, *et al.* Lancet Diabetes Endocrinol. 2014). The safety of LA-PAS was consistent with its known profile.

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AEP597

High usage of drugs for neuropsychiatric morbidity in patients with Cushing´s disease before diagnosis and at 5–10 years follow-up – a nationwide study

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Background
Neuropsychiatric symptoms and cognitive dysfunction are common in Cushing´s disease (CD), and seem only partly reversible after biochemical remission has been achieved.
Aim
To investigate prescription of drugs associated with neuropsychiatric morbidity in a large national cohort of CD patients.
Methods
Patients in the Swedish Pituitary Registry, diagnosed with CD between July 2006 and January 2018 were included, $n=179$ (139 women), median age at diagnosis 45 years (range 11–81). Each CD patient was matched with four controls from the background population, by sex, age and living area. Data on dispensed antidepressants, sleeping pills/tranquilizers, opioids, anti-hypertensive and anti-diabetic drugs including insulin was collected from the Swedish Prescribed Drug Registry. Dispense of each drug was investigated from 5 years before diagnosis, during active disease, and at 5- and 10-year follow-up. Chi-square and logistic regression analyses were employed.
Results
In active disease 30% of CD patients vs 16% of controls were on antidepressants, OR 2.29, (95% CI 1.57–3.35); sleeping pills/tranquilizers 32% vs 10%, OR 4.16 (2.80–6.17); opioids 49% vs 12%, OR 6.75 (4.67–9.75). 130 CD patients (remission $n=110$, not remission $n=16$, remission status unknown $n=4$) were available for a 5-year follow-up. Use of antidepressants remained high, 27% in all CD patients regardless of disease control (in remission 26%), sleeping pills/tranquilizers, 24% (in remission 23%) and opioids, 35% (in remission 35%), whereas use of anti-diabetic drugs decreased from 28% at diagnosis to 13% (in remission 13%), RAS-blockade from 56% to 28% (in remission 25%), Ca-antagonists from 38% to 12% (in remission 8%). At 10-year follow-up of CD in remission ($n=52$), use of antidepressants and sleeping pills/tranquilizers still remained high, 25% and 21% respectively. In subjects eligible for analysis *before* diagnosis (CD $n=103$, controls $n=412$), 32% of CD vs 17% of controls, OR 2.39 (1.46–3.89) had been prescribed an antidepressant on at least one occasion; sleeping pills/tranquilizers 24% vs 17%, OR 1.62 (0.96–2.73); opioids 49% vs 25%, OR 2.91 (1.86–4.54). Notably, the CD vs control difference in use of antidepressants was apparent already 5 years before CD diagnosis.
Conclusions
This prospective registry study shows that a high rate of patients with CD were on drugs for neuropsychiatric morbidity and pain from at least 5 years before diagnosis. Regardless of remission status the rate remained high, suggesting non reversible effects on mental health and a need for long-term follow-up.

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AEP598

The importance of DHEA-S levels in cushing's syndrome; is there a cut-off value in the differential diagnosis?

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Purpose
To evaluate the relationship between basal dehydroepiandrosterone-sulfate (DHEA-S) levels and other tests used in the diagnosis and differential diagnosis of Cushing's Syndrome (CS) among the patients with pathologically confirmed CS.
Methods
In this multicenter study, the data of 623 patients with CS were evaluated retrospectively. The patients were classified as Group 1 ($n=353$ Cushing's disease;CD), Group 2 ($n=242$ adrenal CS) and Group 3 ($n=28$ ectopic ACTH syndrome; EAS). The groups were compared in terms of demographic data, estimated duration to diagnosis of CS, pre-operative ACTH, basal cortisol, DHEA-S, 24-hour urinary free cortisol (24 h-UFC) levels and dexamethasone suppression test (DST) results. Correlations between DHEA-S levels and all parameters were evaluated. A ROC curve was produced to calculate the optimal DHEA-S cut-off value in the differential diagnosis of CS. The effectiveness of the calculated DHEA-S cut-off level in demonstrating the accurate etiology of patients with gray zone in terms of ACTH levels (10–20 pg/ml) was assessed.
Results
The Group 1 patients were younger than the Group 2 patients ($P<0.001$), while Group 3 had more male patients than the others ($P<0.001$). Basal cortisol, ACTH, 24 h-UFC levels were significantly different between the three groups (Group 3>Group 1>Group 2), ($P<0.001$, for all comparisons). The DHEA-S level was significantly lower in Group 2 compared to the other two groups ($P<0.001$), while Group 1 and Group 3 had similar DHEA-S levels. There was a negative correlation between DHEA-S levels and age at diagnosis ($r=–0.184$, $P<0.0001$) and high-dose DST ($r=–0.133$, $P<0.0001$); and a positive correlation between basal cortisol ($r=0.247$, $P<0.0001$), ACTH ($r=0.550$, $P<0.0001$) and 24 h-UFC levels ($r=0.172$, $P<0.0001$).No significant correlation was found between DHEA-S levels and other parameters. The optimal cut-off DHEA-S value that providing differential diagnosis of CS was calculated to be 43.2 µg/dl [sensitivity of 88%(79–93%) and specificity of 76% (70–82%)] between Group 1 and Group 2. This DHEA-S cut-off level demonstrated the accurate etiology in 93% of 14 CD and 100% of 44 adrenal CS in patients with gray zone in terms of ACTH levels. The optimal DHEA-S cut-off value that providing differential diagnosis of CS was calculated to be 136.5 µg/dl [sensitivity of 91% (87–98%) and specificity of 73% (69–81%)] between Group 2 and Group 3. No significant cut-off level was found between Group 1 and Group 3.
Conclusion
This study showed that the DHEA-S cut-off value could be used for differential diagnosis of CD and adrenal CS with high sensitivity and specificity, at the initial evaluation.

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AEP599

Midparental height is an important predictive parameter in a late diagnosis of acromegaly and gigantism in adults. Single centre, pilot study

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Introduction
Acromegaly is a rare disorder caused by excessive growth hormone production. Common clinical manifestations are visual changes as well as serious systemic complications. In childhood and adolescence, excessive growth hormone production leads to abnormal tall stature. To date, only a few studies have been published focusing on analysing the growth of patients with acromegaly, in particular regarding the growth of their parents and siblings. A single report (Perheentupa *et al.* 1986) suggested, that acromegalic patients came from high-growth families. The aim of this study is to test the relationship between the tall stature related to midparental height (MPH) and clinical features, the onset of diagnosis and comorbidities.
Methods
This is a pilot, one centre cohort study conducted in 2019 among adult acromegalic patients with no family history of pituitary adenoma. Patients were analysed in 2 subgroups depending on body height: normal stature and tall stature defined as body height above 97 percentile for sex, age, and ethnicity or >1.5 standard deviation (s.d.) from MPH. The structural anamnesis including e.g. data on parents/siblings/patient's body height was collected during a routine outpatient clinic visit.
Results
Among 100 consecutivepatients interviewed in the outpatient clinic, full data were available from 26 males (43%) and 34 females (57%) with a mean age at the diagnosis 46 years (19–75). Retrospectively 14 patients (23%) presented features of acrogigantism: 15% met criteria of gigantism, whereas 8% presented tall stature. Acrogigantism patients were significantly younger (33.64±10.74 vs 50.24±14.15 years) with concomitant hypogonadism (64.29 vs 26.83%), greater tumour size (21 vs 12 mm) and higher growth hormone concentration (62.5 vs 21.8 uIU/ml) in comparison to normal stature patients (<0.05). In acromegalic patients with normal stature father's height (–0.37±0.97 s.d.) and mother's height (–0.82±0.96 s.d.) were smaller in comparison to the polish population mean ($P<0.05$). Only female siblings' height in both groups and mother's height in tall stature group were above the polish population mean but not statistically significant.
Conclusion
According to our results, the higher stature of patients with sporadic somatotropinoma might be due to pre-existing unrecognized gigantism in adolescence and it is not associated with primary genetic tallness. Midparental hight is an important predictive parameter in a late diagnosis of acrogigantism.

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AEP600

Phenotypic differences between patients with familial pituitary neuroendocrine tumours due to MEN1 or AIP mutations

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Introduction
Germline *AIP* and *MEN1* mutations are the main known aetiologies of familial pituitary neuroendocrine tumours (PitNETs), which represent 5% of all PitNETs. We compared the clinical and tumour characteristics of *AIP* (*AIP* mut) and *MEN1* mutation-positive (*MEN1* mut) PitNET patients.
Methods
We retrospectively analysed 70 *MEN1* mut and 167 *AIP* mut patients with PitNETs. *MEN1* genetic testing was performed according to currentguidelines, while *AIP* genetic analysis was offered to FIPA patients, as well as

sporadic pituitary macroadenomas with onset <30 yr or micro/macroadenomas with onset <18 yr.
Results
In our *MEN1* mut PitNET cohort, 52.9% were females, age at PitNET diagnosis was 29.6±16.6 yr (mean± s.d.) and 58.6% had a prolactinoma, whereas in the *AIP* mut PitNET cohort, 61.1% were males, mean age at PitNET diagnosis was 24.3±11.9 yr and somatotropinomas predominated (81.4%). *MEN1* mut PitNET patients had lower rates of hypopituitarism at diagnosis (21.4 vs 42.7%; $P=0.011$), fewer macroadenomas (42.4 vs 83.2%; $P<0.001$), extrasellar and suprasellar extensions (28.6 vs 66.7%; $P<0.001$, and 28.6 vs 54.3%; p=0.004, respectively), fewer pituitary deficits at diagnosis (0.3±0.7 vs 0.8±1.1; $P=0.006$) and smaller tumour diameter (14.6±15.0 vs 20.1±13.0 mm; p=0.005), and none had pituitary apoplexy (vs 8.2%; p=0.026) in comparison to *AIP* mut PitNETs. *MEN1* mut PitNET patients required fewer treatments (1.0±1.0 vs 2.1±1.7; $P<0.001$) and fewer operations (0.2±0.5 vs 0.9±0.8; $P<0.001$), less radiotherapy (13.4 vs 32.9%; p=0.003) and fewer multimodal treatments (30.4 vs 67.2%; $P<0.001$), and had a 5.5-fold less active disease at last follow-up (4.7 vs 25.0%; p=0.004) than *AIP* mut PitNETs.
When comparing individual tumour types, *AIP* mut somatotropinomas had higher rates of macroadenomas (90.0 vs 51.7%; $P=0.009$), extrasellar extension (75.7 vs 25.0%; $P=0.026$) and required more operations (1.1±0.8 vs 0.4±0.5; $P=0.009$) than *MEN1* mut somatotropinomas, and showed a trend for more cavernous sinus invasion (41.9 vs 0%; $P=0.096$). *MEN1* mut prolactinomas had lower pituitary apoplexy rate (0 vs 16.7%; $P=0.016$) and a trend for lower rates hypopituitarism at diagnosis (30.3 vs 62.5%; $P=0.090$) with fewer pituitary deficiencies (0.5±0.9 vs 1.4±1.5; $P=0.066$), and fewer operations (0.2±0.4 vs 0.4±0.5; $P=0.072$) than *AIP* mut prolactinomas. NF-PitNET did not differ between *MEN1* mut and *AIP* mut patients, except regarding age at first symptoms (higher in MEN1 subgroup, 53.5±5.0 vs 22.6±7.7 yr; $P=0.040$).
Conclusions
*AIP*mut PitNETs are in general more aggressive than *MEN1*mut PitNETs. This is dominated by more aggressive disease in *AIP*mut prolactinomas and somatotropinomas compared to *MEN1*mut prolactinomas and somatotropinomas, while *AIP*mut and *MEN1*mut NF-PitNETs (some of those possibly representing incidentalomas) may show an indolent course of disease and often require no treatment.

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AEP601

A case of wolfram syndrome with primary hypogonadism

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Introduction
Wolfram syndrome, is a rare autosomal recessive genetic disorder that is characterized by diabetes mellitus (DM), diabetes insipidus (DI), optic atrophy, and sensorineural deafness as well as various other possible disorders. DM is the first manifestation, and optic atrophy also onsets in the first decade of life. The onsets of DI and sensorineural deafness are in the second decade, urinary tract abnormalities are in the third decade, and neurologic abnormalities are in the fourth decade, respectively. Hypogonadotropic hypogonadism is a usual manifestation of the syndrome; however, as in the present case, primary hypogonadism can be rarely seen. Herein, we aimed to present a case of Wolfram syndrome with primary hypogonadism.
Case report
A 25- year old male patient admitted to our clinic with complaints of polydipsia, polyuria, and mouth dryness. The onset of DI and optic atrophy was at the age of thirteen and started desmopressin therapy. He was diagnosed with DM at the age of fourteen, and intensive insulin therapy was instituted subsequently. His polyuria and polydipsia complaints continued even at times with oral desmopressin treatment when his blood glucose levels were at normal values. The patient's laboratory tests revealed sodium:148 mEq/l (136–146) urine density:1005.In the hormonal panel; FSH: 33.4 IU/l (1.5–12.4), LH: 30.9 IU/l (1.7–8.6), total testosterone: 335 ng/dl (280–800). Serum IGF-1, ACTH, cortisol, TSH, free T4 levels were normal. Desmopressin (melt) dose was eventually titrated up to a 360 mg bid. Even with this dose, he was putting out 4 liters of urine daily. Therefore oral desmopressin therapy stopped, and desmopressin was started ten mg intranasally at three times a day. After intranasal desmopressin, his urine output decreased, and serum sodium gradually improved to 140 mmol/l. In the hypophysis MRI, gland dimensions were normal, and there were neither adenoma nor cystic lesions. In the scrotal ultrasonography, bilateral testicles were in the scrotum, and the sizes were slightly smaller than normal. Spermiogram analysis was revealed compatible with azoospermia. There were no trauma, surgery, infection, or cytogenetic defect history that could be related with primary hypogonadism. So primary hypogonadism was accepted as a component of Wolfram syndrome.
Discussion
As in the present case, the patients diagnosed with Wolfram syndrome requires long-term follow-up because of the various clinical disorders that can occur over the years. Primary hypogonadism should be kept in mind in case of symptoms and signs of hypogonadism at Wolfram syndrome.

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AEP602

Effect of silibinin on acth synthesis and secretion in human adenomatous corticotropes *in vitro*

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Silibinin, a milk thistle extract with known hepatoprotective effects, has recently been shown to act upon tumoral corticotropes and revert the Cushingoid phenotype in an allograft mouse model (Riebold *et al.* 2015). Silbinin is known to inhibit HSP90 -a chaperone to the glucocorticoid receptor-thereby restoring sensitivity to glucocorticoid negative feedback in tumoral corticotropes. Aim of the present study was to assess the effect of silibinin on ACTH synthesis and secretion by human corticotrope adenomas *in vitro*.
Methods
Eight human ACTH-secreting pituitary adenomas were collected during surgery and established in culture as per our protocol (Pecori Giraldi *et al.* 2011). Specimens were treated with 10–50 µM silibinin for up to 72 hours. ACTH medium levels were measured by Elisa; *POMC* expression was assessed by RT-PCR (Cassarino *et al.* 2017).
Results
Silibinin reduced spontaneous ACTH secretion to a variable extent in individual adenomas: from 32 to 79% of baseline at 4 h, and 54–85% of baseline at 48 and 72 h. Silibinin was also effective in reinstating or enhancing sensitivity to steroid negative feedback: ACTH decreases during 10–50 µM silibinin incubation ranged from 10 to 63% of dexamethasone-treated wells at 4 hours, 70–80% at 48 hours and 36 to 80% at 72 hours, indicating long-lasting effect on glucocorticoid sensitivity. Silibinin induced a variable decrease in *POMC* expression, both as regards expression in control and dexamethasone-treated wells; some specimens exhibited a marked sensitivity to the inhibitory effect, with *POMC* expression decreasing to less than 50% of control.
Conclusions
This data suggests that silibinin can inhibit ACTH secretion and *POMC* synthesis and restore sensitivity to negative glucocorticoid feedback.
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AEP603

TGF-β increases caspase 3 activation and migration in bronchial carcinoids

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Introduction
Typical and atypical bronchial carcinoids (TBC and ABC) are well-differentiated neuroendocrine neoplasms (NEN). First-line treatment is radical removal of the primary tumour; however, management of metastatic BC is still challenging. Bronchial carcinoids (BC) may benefit from treatment with mTOR inhibitors, although response rates are moderate. TBC have shown reduced sensibility to mTOR inhibitors respect to ABC, notwithstanding its less aggressive behaviour. PI3K/AKT/mTOR crosstalk with TGF-β has been reported and could explain the differential sensitivity of BC to treatment. Previous studies have reported TGF-β's ability to activate mTOR pathway and induce epithelial to mesenchymal transition (EMT), affecting cell survival, proliferation, migration and invasiveness.
Aims
The present study focused on understanding the possible crosstalk between TGF-β signalling and PI3K/AKT/mTOR in BC.
Materials and methods
Basal levels of TGF-β downstream proteins were analysed by Western blot in BC (4 TBC and 3 ABC). Functional assays (cells viability, migration and caspase 3/7 activation) were performed using TBC *in vitro* cell model (NCI-H727 cell line) after treatment with the mTOR inhibitor everolimus (Eve) at 100 nM concentration and/or 1 pM TGF-β.
Results
TGF-β/SMAD protein levels were higher in TBC vs ABC tissues. Mean differences (% TBC vs ABC) were as follows: TGF-βRI (17.85±5.298; $P=0.007$), TGF-βRII (50.07±23.52; $P=0.04$), Smad 2/3 (536.6±159.9; $P=0.008$). In addition, caspase 3 levels were higher in TBC vs ABC tissues (257.0±131.8, $P=0.03$). In NCI-H727 cells, TGF-β or Eve treatment alone had no effect on cell viability, whereas their combination slightly reduced it by >10% vs control ($P=0.009$) and this effect was not accompanied by apoptosis induction. TGF-β, however, increased caspase activation by 14% vs control ($P=0.04$). Combined treatment with Eve abrogated this effect. TGF-β induced migration in TBC cell model by 40% vs control, whereas combined treatment with Eve abrogated cell migration, reducing this phenomenon by 27% vs control ($P<0.0001$).
Conclusion
TGF-β/SMAD and PI3K/AKT have major roles in cells pathophysiology and have been reported to be activated simultaneously in advanced states of tumorigenesis. We report an increased expression of TGF-β/SMAD proteins as well as enhanced caspase activation in TBC cells. The interplay between these pathways could explain TBC increased resistance to medical therapy by inducing EMT. Combined treatment with the mTOR inhibitor Eve abrogated TGF-β induced EMT and, therefore, inhibition of TGF-β/SMAD and PI3K/AKT/mTOR pathways could potentially reduce tumour malignancy in these cells.

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AEP604

Salivary cortisol and cortisone – Effects of liquorice and blood contamination

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Context
Late-night salivary cortisol is a recommended screening method for Cushing's syndrome. Liquorice intake may lead to falsely elevated salivary cortisol as glycyrrhizic acid inhibits the 11β-hydroxysteroid dehydrogenase type 2 induced conversion of cortisol to cortisone in the salivary glands. Furthermore, sample contamination by blood from the oral mucosa may also cause falsely elevated salivary cortisol levels. Salivary cortisone has been suggested to more closely reflect free plasma cortisol and is less likely to be affected by these preanalytical errors.
Objective
To determine if (i) liquorice consumption significantly increases late-night salivary cortisol levels, and if so, what dose is required for this to happen and how long wash-out period is required for salivary cortisol levels to normalize; (ii) what level of blood contamination lead to significantly increased salivary cortisol levels.
Design
Thirty healthy volunteers abstained from liquorice for four weeks prior to the study. Participants were randomized to a low, medium or high dose of liquorice, corresponding to a daily glycyrrhizic acid dose of 1.5, 3.0 or 6.0 mg/kg body weight. Saliva samples were collected during five days of baseline sampling, one week of daily liquorice consumption and four weeks of wash-out. Another sixteen healthy volunteers collected both saliva and blood samples, which were mixed to achieve a graded blood contamination of the saliva. Salivary cortisol and cortisone were analyzed with LC-MS/MS. Blood contamination was quantified using Cobas Hemolysis index (Roche Diagnostics) and by visual examination on a 7-point scale.
Results
Significant increases of salivary cortisol levels were observed during the seven days of liquorice intake in the medium and high dose groups (median increase 66% and 137%, respectively). The salivary cortisol levels returned to baseline four days after liquorice withdrawal in both groups. Salivary cortisol increased significantly by a 0.5% blood contamination. Visual grading corresponded very well to hemolysis index. Salivary cortisone levels were not affected by liquorice consumption or blood contamination.
Conclusion
Liquorice intake equivalent to a glycyrrhizic acid dose of 3–6 mg/kg body weight, corresponding to a daily intake of 100 g liquorice candy for a 70 kg person, causes a significant increase in late-night salivary cortisol levels. This effect weans off after four days. Saliva samples with a blood contamination of 0.5% leads to significantly increased salivary cortisol levels. Visual screening is sufficient to exclude significantly blood contaminated samples. Salivary cortisone levels are independent of both these preanalytical errors.

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AEP605

An education programme for patients with pituitary tumours and their relatives; preliminary results

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Background
Patients with pituitary tumour live with life-long consequences of their disease. The first year after pituitary surgery represents a time period of symptoms, fear of tumour recurrence, existential concerns as well as extensive medical evaluations and decisions about hormone replacement. To increase wellbeing, a person-centred care practice up to 1 year after pituitary surgery covering self-management support, accessibility and continuity has been implemented and are under current evaluation. One part of this practice an education programme for patients and their relatives has been implemented.
Aim
To evaluate an education programme within a person-centred practice for patients with pituitary tumours and their relatives.
Method
After pituitary surgery all patients at a specialist endocrine clinic are offered a one-time education programme six-nine months after surgery. The content was developed in collaboration with patients and an interdisciplinary pituitary team. Specific content comprise surgery, tumour recurrence, medical evaluation and treatment, symptom and signs, health and quality of life with information from neurosurgeons, endocrinologists and specialist endocrine nurses. The education includes discussions on common experiences and skills needed to manage different symptoms in daily life. After participation patients are asked to complete a questionnaire with structured and open response alternatives on the benefit of participation and what could be added to the programme.
Findings
During one year 39 patients were invited and 33 attended. Participants were 26 to 81 years and 1/3 brought a relative. Totally, 27 patients completed the evaluation (82% response rate). All responders reported that the education

was meaningful. The peer-support and the medical information were rated equally important. Respondersreported that they felt comfortable in the group, but some thought should be more discussion among patients supported by physician and nurses. Some wanted more individual information from the other participants such as tumour type. The majority stated that they have gained new or more in-depth knowledge. Most participants thought the timing of the information after surgery and treatment was good. A few participants expressed a need to havethis type of information before surgery.
Conclusions
A pituitary tumour school can be a way to provide patients with more knowledge about their illness as well as an opportunity to exchange experiences. The time 6–9 months after the surgery was considered appropriate based on the participators evaluation.

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AEP606

Clinical picture and MRI findings in patients with hypophysitis – a single-centre experience

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Hypophysitis is a rare clinical condition manifesting as pituitary dysfunction: hypopituitarism or diabetes insipidus (DI) and pituitary enlargement causing mass effect (headaches, visual disturbances) due to the inflammation of the pituitary gland. We conducted a retrospective analysis of medical records of patients diagnosed with hypophysitis in the Department of Endocrinology of the Bielanski Hospital from 2014 to 2019. Twenty-five patients were identified, which represents 0.3% of all patients hospitalized at the Department during that period. Women predominance was noted (80% females and 20% males) and a mean age of patients was 40.6 ± 16.2 years. No association with pregnancy and labour was present except for one patient. Primary hypophysitis was suspected in most cases. Secondary hypophysitis was recognized in 3 patients – one with Langerhans cell histiocytosis and two immunotherapy induced. Diagnosis was based on clinical picture, hormonal and imaging results. No histopathologic confirmations were available in 23 cases. The most common symptoms at presentation were headaches and DI (52% of cases each). Anterior pituitary dysfunction was frequently present – at least one tropic hormone deficiency was found in 60% of patients. Gonadotroph deficiency was the most frequent (48%), followed by TSH and ACTH deficiencies (in 44% and 40%, respectively). Panhypopituitarism was present in 7 cases (28%) and in 5 of those accompanied by DI. Hyperprolactinemia occurred less frequently, in 20% of cases. Visual disturbances caused by optic chiasm compression/infiltration or cranial nerves palsies were present in 9 cases (36%). The most frequent finding on MRI scans was the lack of posterior lobe bright spot ($n = 14$, 56%). Pituitary stalk thickening, pituitary enlargement alone or together with stalk thickening were present in 9 (36%), 7 (28%) and 7 (28%) cases, respectively. In one patient a unilateral internal carotid artery occlusion was found and in another patient the inflammation extend to hypothalamus. Nine patients with visual disturbances and severe headache were treated with high-doses of glucocorticosteroids with partial or complete resolution of symptoms, but in 4 patients relapses were observed.
Conclusion
Hypophysitis typically occurs in middle-aged woman without relationship to recent pregnancy. The most frequent symptoms at presentation are headaches and DI. The most common anterior pituitary deficiency is a gonadotroph deficiency, not isolated corticotroph deficiency as previously stated. High-dose glucocorticosteroids treatment exerts a positive effect in the form of at least partial relief of symptoms, especially headaches.

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AEP607

Data mining analyses for precision medicine in acromegaly

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Since the first somatostatin receptor ligand (SRL) was used to treat acromegaly, predicting which patients could benefit from their use has become crucial to avoid months of ineffective treatment for non-responding patients. Although many biomarkers linked to SRL response have been identified, there is no consensus criterion on how to prescribe according to biomarker levels. In this study, we evaluate previously reported biomarkers using more exhaustive and accurate methods than those used in previous analyses to provide better predictive tools from the data. Using advanced mathematical modelling and artificial intelligence, a more accurate acromegaly patient stratification was obtained regarding their ability to respond to SRL. Our results show an association between extrasellar growth and high BMI for SRL non-responding patients. Furthermore, we provide different models of patient stratification. The mathematical algorithms generated achieved a much higher cross•validatedaccuracy when the population is fragmented according to relevant clinical characteristics. Considering all the models, we proposed a patient stratification based on the extrasellar growth of the tumor and the expression of E-cadherin, *GHRL*, *IN1-GHRL*, *SSTR5* and *RKIP* with accuracies that stand between 71 to 95%. This new strategy of data mining is necessary if we want to implement personalized medicine in acromegaly and requires an interdisciplinary effort between computer science, mathematics, biology and medicine. This new methodology opens a door to more precise personalized medicine for acromegaly patients.

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AEP608

Metabolism of glucose in patients with acromegaly treated with Pegvisomant and/or Pasireotide LAR after resistance to first generation somatostatin receptor ligands

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Introduction
Acromegaly (Acro) is characterized by insulin sensitivityreduction, glucose intolerance (IGT) and diabetes mellitus (DM2 in 15%–38% of patients). Studies that investigated action of medical therapies for acro on glucose metabolism, didn't provide conclusive data. Association between blood glucose (BG) levels and serum IGF-I levels in patients with DM2 and acro has been suggested, however,IGF-I levels and hemoglobin A1c (HbA1c) correlation is still controversial due tomultifactorial influence.

Study aim
Investigate in a large retrospective cross-sectional multicenter study glucose metabolism in patients with acro resistant to 1st gen somatostatin receptor ligands (SRLs) treated with Pegvisomant (Peg) or Pasireotide LAR (Pasi).
Patients and methods
Consecutive patients enrolled per following inclusion criteria: (1) resistance to 1st gen SRLs (2) treated with Pasi or Peg both for at least 6 consecutive months. Exclusion:patients with treatments influencing glucose, exception being glucocorticoid replacement. Biochemical control of acro was defined as normal IGF-I.
Results
72 patients with active Acro: mean age 37 yrs (S.D.:15). 47 females (65.3%); 28 (38.9%) treated with Pasi and 44 with Peg (61.1%). Peg was monotherapy in 18 patients (40.9%) and combo with 1st generation SRLs 26 patients (59.1%). The number of patients with IGT and DM2 was superimposable between the 2 groups (Pasi and Peg-V). In Pasi group, 19 patients had acro control (67.9%); glucose metabolism worsened in 16 (57.1%). Worsening of glucose metabolism occurred most frequently in patients with persistently active acro (62.5%) and with higher BG and HbA1c at study start. Likewise, HbA1c was higher in patients with active acro, although HbA1c worsened during Pasi treatment both in euglycemic and IGT at study entry, regardless of normal IGF-I. In Peg group, 31 patients reached normal IGF-I (73%); glucose worsened in 12 (27.3%) but improved in 5 patients (11.4%). All patients who experienced glucose improvement had controlled acro, regardless of the combo use. Among 13 patients with active acro, BG worsened in 5 (38.4%). Patients with worsening BG control had higher HbA1c ($P=0.03$) and required higher Peg doses (mean 25 mg/day S.D.: 10; $P=0.04$). Patients with higher HbA1c had higher IGF-I, both at entry and study endand were treated with higher Peg dose (mean 25 mg/day).
Conclusion
We suggest that glucose abnormalities in patients treated with Peg (either mono or combo with 1st generation SRLs) or Pasi are dependent on both pre-treatment BG and persistence of active acromegalyand require close monitoring.

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AEP609

Biliary stone disease in acromegaly under somatostatinanalogues: A longterm safety study

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Introduction
Somatostatin analogues (SSA) are one of the main effective drug used in acromegaly. Sludge and/or cholelithiasis development represents oneof the more common side effect. The aim of the study was to analyze the frequency of biliary adverse events (BAE) and possible predictive factors, to propose a work-up strategy for their management.
Method
This is a single centre, longitudinalretrospective study; we enrolled 91 acromegaly patients during SSA for at least one year. We evaluated biochemical markers of acromegaly (GH, IGF-1 e IGF-1/ULN) at diagnosis, at BAE onset or at last follow up. We also collected type, dose andduration of SSA, glucose and metabolic profile at diagnosis and follow up. For the detection of sludge/gallstone disease, an ultrasound was performed yearly. In patients developing BAE we evaluated ursodeoxycholic acid (UDCA)effectiveness.
Results
We divided patients into 4 groups: no BAE(G–); positive history for BAE (G+), cholelithiasis ($G+_{ch}$) and only sludge ($G+_{sl}$). 61,5% of patients developed at least one BAE (58.9% cholelithiasis and 41.1% only sludge). No differences between lanreotide, octreotide and pasireotide were found. Only five patients underwent cholecystectomy for symptomatic cholelithiasis. None of metabolic markers proved to be associated with BAE. All GH, IGF-I and IGF-1/ULN proved to be lower in $G+_{ch}$, compared to $G+_{sl}$, ($P=0.001$).Kaplan-Meier curve showed that 50% of subjects developed BAE within 5 years from the SSA start. In 71% of subjects with BAE,UDCA treatment was started; 60% had a complete resolutionwithout recurrence, while 40% did not benefit from therapy. The UDCA clinical efficacy was statistically greater in $G+_{sl}$ than in $G+_{ch}$ (regression in 88% of cases versus 30%; $p=0.0009$). The regression of BAE occurred after 12 months of therapy. Analyzing the Kaplan-Meier curve of the UDCA efficacy, it can be observed that in 50% of the subjects the BAE resolved after 5 years of therapy.
Conclusion
biliary stone disease is a frequent SSA adverse event, although it is often symptomless. Ultrasound follow-up and early UDCA therapy, represent a valid strategy in their management.

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AEP610

Importance of sexual function assessment in multidimensional evaluation of AGHD patients: Baseline results from the management of adult growth hormone deficiency (MAGHD) study

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Background
Patients with adult growth hormone deficiency (AGHD) have impaired health-related quality of life (QoL). While the effects of reduced muscle mass and vitality-loss on QoL have been well characterized in AGHD, the impact of AGHD on sexual function, a recognized factor influencing well-being, has never been deepened.
Aim
To investigate the prevalence of sexual dysfunction in AGHD patients referring to a single endocrinological center and grouped according to their history of r-hGH therapy.
Methods
The MAGHD Study aims to improve management of AGHD patients through a smartphone app (MAGHD-App) and a fit-watch. The 83 enrolled patients (31 Females, 52 Males, mean age 56.27 ± 14.68 years) were divided in 3 groups (G) according to r-hGH therapy: on long-term treatment (G1, $n=32$), previously treated (G2, $n=20$), never treated (G3, $n=31$). At the baseline visit, besidesclinical and biochemical data, a psychological assessment was performed. IIEF-15 (for males) and FSFI (for females) were employed to evaluate sexual function in addition to QLS-H and QoL-AGHDA routinely used to assess QoL. The nonparametric Kruskal-Wallis test was used for comparison among 3 groups.
Results
According to IIEF-15 results, the prevalence of erectile dysfunction (ED) in AGHD males was 60%. Erectile function (EF) score was significantly higher in G1 compared to G2 and G3 ($P<0.05$) with an ED prevalence of 37.5% in G1, 75% in G2 and 75% in G3. Even excluding interfering factors (serum testosterone <2 ng/ml and age ≥65 years), ED prevalence did not change significantly. Moreover, EF domain was inversely and directlycorrelated to age (R^2 0.130, β–0.360) and IGF1 levels (R^2 0.156, β 0.395), respectively. The prevalence of female sexual dysfunction according to FSFI was 89%. Even though desire, arousal, lubrication and overall scores were significantly higher (better results) in G1 compared to G2 and G3 ($P<0.05$), no correlation resulted between FSFI domains and IGF1 levels. Only an inverse correlation resulted between desire domain and age.
Conclusions
This real-life study documents a high prevalence of sexual dysfunction in AGHD patients, especially in untreated ones, and that r-hGH treatment seems to be associated to better sexual outcomes. These results suggest that the evaluation of sexual function should be integrated into global assessment of AGHD patients since sexual activity is able to influence both well-being and QoL.
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AEP611

Effects of different therapeutic approaches on cardiovascular risk in patients with acromegaly: Results of a multicentric study

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The association between acromegaly and increased cardiovascular morbidity and mortality is widely recognised. The aim of this retrospective multicentric study is to evaluate the impact of different therapeutic approaches on the progression of cardiovascular risk (CVR) in acromegalic patients. At diagnosis and last follow up (follow up time of 13±8 years),we assessed BMI, blood pressure, glycaemic and lipid profile, GH and IGF1 levels in 199 patients with acromegaly (116 females), which received at least a medical treatment during follow up. To assess CVR, we used the Italian Heart Project Score (IHPS-CVR) and Framingham Score (FS-CVR), which were calculated both at baseline and last follow up. During follow up, major adverse cardiac events (MACEs) were recorded in 16 subjects. We divided patients in two groups according to received treatment: 60 patients treated only with medical therapy (MT) and 139 with a combination of medical therapy, neurosurgery and, in some cases, radiotherapy (MT+NS±RT). At baseline, MT patients were older ($P<0.001$), with higher prevalence of diabetes and hypertension ($P<0.001$), and had greater IHPS-CVR (P 0.002) and FS-CVR values ($P=0.004$), whereas the MT+NS±RTgroup showed higher GH levels ($P=0.023$) and largest pituitary adenomas ($P<0.001$). To adjust for these differences in the comparison of the 2 groups, we computed a propensity score using the clinical characteristics that differed at baseline as covariates for a logistic regression model. With an inverse probability weighting (IPW) we created a focused sample that allows for unbiased estimates of treatment effects. In our cohort, the estimated time-related profiles of CVR remain approximately constant over time in both groups. In addition, MT and MT+NS±RT groups appeared comparable regard to both IHPS-CVR and FS-CVR without any statistically significant differences at baseline (IHPS-CVR IC 95% : –4.38+2.68; FS-CVR IC 95% : –7.35+9.42) and at 10 years of follow up (IHPS-CVR IC 95%: –5.36+2.95; FS-CVR IC 95% : –9.92+8.12). Furthermore, MT and MT+NS±RT groups did not significantly differ for MACEs incidence rate (P 0.11). Finally, univariate analysis adjusted for gender, age and IPW showed that diastolic hypertension (P 0.008) and disease control (P 0.011) were the most significant risk factors for MACEs. In conclusion, this study suggests that treatment of acromegaly is able to slow the CVR progression although increasing age during follow-up, regardless the type of the therapeutic approach. The disease control significantly impacts on the cardiovascular risk, but also diastolic hypertension control could be an important therapeutic target to reduce the MACEs incidence.

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AEP612

IGF-I variability and its association with demographic and clinical characteristics in patients with acromegaly treated with injectable somatostatin receptor ligands (SRLs); results from OPTIMAL, an international prospective phase 3 study

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Background

Most patients responding to injectable somatostatin receptor ligands exhibit IGF-I variability around the upper limit of normal (ULN) during long-term follow up. These fluctuations are thought to result from assay variability, nutrition, comorbid conditions, concomitant medications and other unknown factors. The magnitude and factors affecting this variability arenot well understood in patients with acromegaly treated with injectable SRLs.

Methods

IGF-I levels of patients responding to and stably treated with injectable SRLs were measured over time in the CHIASMA OPTIMAL phase 3 study. Two time periods were assessed – Period 1, three assessments during screening before randomization to octreotide capsules ($n=56$); and Period 2, multiple assessments up to week 36, in patients rescued with SRL injections for ≥12 weeks ($n=21$).Time from last injection to each assessment in period 1 [Screening visits 1 and 2 (SV1 & SV2) and Baseline] was on average 6.8±10.7 (S.D.), 15.8 ±2.7, and 29.0±1.8 days, respectively. Correlation with demographics and Baseline characteristics including age, gender, weight, BMI, and residual tumor size to IGF-I variability was assessed. Percent change for each individual patient from Minimal to Maximal IGF-I values within each period was computed. The overall population mean was calculated (lowest value as the denominator and all other values as a percentage above this value).

Results

Overallmean within-patient percent change of IGF-I levelsduring Period 1 was 20.48±15.56 (range: 0.6–81). Mean IGF-I levels for SV1, SV2 and Baseline were 0.78±0.18,0.79±0.18, and 0.85±0.22 × ULN respectively. Overall increase in mean IGF-I levels from SV1 to Baseline (longest time interval) was statistically significant ($P=0.0002$; paired T-test). Overall mean within-patient percent change of IGF-I levels during Period 2 was 15.27±12.20 (range: 0–41.5). Mean duration of follow up during this period, after patients were already treated for 12 weeks with oral SRL, was 4.38 months (range: 2.67–7.47). The variability in Period 2 was similar to that observed in the entire sample evaluated in Period 1. No significant correlation was found between individual IGF-I percent change and any demographic and Baseline characteristics examined.

Conclusion

IGF-I levels fluctuate in patients with acromegaly responsive to injectable SRLs. These fluctuations can be up to 81% higher than the lowest (most controlled) value, with an average increase of approximately 20%. Significant IGF-I increases were observed at the end of the injection interval of long acting SRLs.

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AEP613

Analysis of adverse events in adult patients with acromegaly receiving oral octreotide capsules: Results from the phase 3, randomized, double-blind, placebo-controlled optimal study

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Background

Distinguishing non-specific signs/symptoms of acromegaly from treatment-emergent adverse events (TEAEs) in patients treated with somatostatin receptor ligands has proven difficult given limited data from placebo-controlled studies. The CHIASMA OPTIMALstudy provides a novel data set to evaluate the incidence of adverse events (AEs) in patients randomized to oral octreotide capsules (OOC) or placebo.

Methods

A multinational, randomized, placebo-controlled study was conducted in 56 adult patients with active acromegaly. Eligible patients had active disease (IGF-1 ≥ 1.3 ×ULN after last pituitary surgery) and an average IGF-1 ≤ 1.0 ×ULN in response to a stable dose of somatostatin analog injection. Patients were randomized (28/group) to OOC or placebofor 36 weeks, followed by an optional open-label extension for up to 1 year. Safety and tolerability were evaluated based on incidence of AEs, including incidence of new or worsening adverse events of special interest (AESIs).

Results

In this study, the safety profile of OOC was consistent with the known safety profile of injectable octreotide. No new safety signals were detected. Nearly all patients (55/56) experienced a TEAE (28 patients [100.0%] in the OOC group and 27 patients [96.4%] in the placebo group). Thirty-three patients (58.9%) experienced a TEAE considered to be related to study drug by the

blinded PI (64.3% of OOC group [18 patients, 40 events] and 53.8% of placebo group [15 patients, 41 events]). TEAEs with an incidence ≥5% that were more common in the OOC group vs placebo group included GI disorders, increased blood glucose, sinusitis, osteoarthritis, and cholelithiasis. TEAEs with an incidence ≥5% that were more common in the placebo group vs OOC group included arthralgia, headache, fatigue, hyperhidrosis, and peripheral swelling. GI disorders were the most common TEAE, reported in 64% of all patients (36/56) and at similar rates between the OOC (68%) and placebo (61%) groups. AESIs (defined as new or worsening signs of acromegaly) were observed in 15 patients (53.6%, 34 events total) in OOC group and in 26 patients (92.9%, 82 events total) in placebo group.
Conclusion
In this study, the safety profile of octreotide capsules was consistent with the known safety profile of injectable octreotide. Most patients receiving octreotide capsules or placebo demonstrated TEAEs, although the profile of most common TEAEs varied between groups. TEAEs observed in the placebo group may be indicative of underlying disease activity. Further analysis may elucidate the difference between treatment related AEs and signs/symptoms of active disease in acromegaly.

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AEP614

The effects of silent pituitary adenomas on pregnancy

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Silent pituitary adenomas are defined as a group of adenomas that are hormonally inactive and do not show clinical signs and symptoms of excess hormones. Data in the literature indicate that fertility is usually affected in women with silent pituitary adenomas.
Aim
To investigate the possible effects of silent pituitary adenomas on pregnancy.
Patients and Method
Thirty patients followed by silent pituitary adenoma, without hormone deficiency or excess, not receiving medical treatment were included in the study. Anterior pituitary hormone levels, follow-up periods, pituitary magnetic resonance imaging findings, number of gravidity, parity, abortus, ectopic pregnancy, stillbirths, presence of symptoms associated with adenoma size increase during pregnancy, adverse pregnancy outcomes, induction of labor history, delivery procedures, pregnancy week at delivery, birth weight, lactation duration were evaluated.
Results
The mean age of the patients was 41.26±9.06 years and the mean duration after the diagnosis was 92,8 months. Of the 30 patients with silent pituitary adenoma, 7 were followed by macroadenoma and 23 with microadenoma. Among all 92 pregnancies, 66 resulted in live births. No statistically significant difference was found between pregnancy week at delivery, birth weight, lactation duration in live births in macroadenoma and microadenoma groups. However, there was a statistically significant difference between the two groups with respect to adenoma size, the incidence of nausea-vomiting and visual impairment during pregnancy were more prominent in macroadenoma with respect to microadenoma ($P=0.016$ and $P=0.042$, respectively).
Discussion
Elective abortion, missed abortion, stillbirth, live birth rates and lactation duration are thought to be similar to the general population. In our study, spontaneous pregnancy rates were found to be high and no negative effects of silent pituitary adenomas on fertility were observed. Although rarely reported in the literature, there is an increase in the size of silent pituitary adenomas during pregnancy, however, no adenoma growth confirmed by MRI was observed in our study. In terms of pregnancy-related complications, silent pituitary adenoma was not associated with increased risk compared to the general population and there was no obvious negative effect on fetal development. Despite the high cesarean section rates in our country, silent pituitary adenomas were not associated with an increased cesarean section rate in our study. In conclusion, when the present findings are evaluated together, it is not possible to mention that the patients followed up with silent pituitary adenoma have negative effects on pregnancy outcomes, fetal development, and lactation.

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AEP615

Cushing's syndrome negatively affects socio-economic variables many years before the diagnosis: A nationwide registry-based cohort study

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Introduction
Cushing's syndrome (CS) results from prolonged glucocorticoid excess. Both iatrogenic and endogenous CS cause somatic and neuropsychiatric morbidity that do not fully reverse after biochemical disease control. However, the real-world socio-economic consequences for patients and their families are largely unknown.
Aim
To determine the impact of CS on work status, income, education, marital status, parenthood, and depression before and after treatment.
Design
A nationwide registry-based cohort study.
Methods
Using the Danish health registries, we identified 411 patients diagnosed and operated for benign pituitary or adrenal CS between 1986–2017. Pituitary/adrenal ratio was 1.16. We matched each patient with ten persons from the background population of same sex and age (the reference population). We obtained registry data on socio-economic factors and anti-depressive medication, and followed them from up to ten years before diagnosis to ten years after surgery. We calculated crude and adjusted relative-risk (RR) of patients in working age returning to fulltime work two years after surgery using a modified Poisson regression.
Results
During a median follow-up of 13.4 years (5516 person-years), 20% ($n=84$) of CS patients and 11% ($n=454$) of reference population had died ($P<0.001$). Compared to the reference population, we found that fewer patients were in a fulltime job from seven years before diagnosis [68.2% vs 74.6%, $P=0.03$] to ten years after surgery [50.0% vs 70.3%, $P<0.001$] with the biggest difference observed the year after surgery [33.1% vs 72.2%, $P<0.001$]. Mean annual income was decreased by 6300 EUR (CI 95% 3400–9200) in the years after surgery. More patients were prescribed antidepressant drugs from six years before diagnosis [10% vs 5%, $P=0.004$] and up to ten years after surgery [16% vs 9%, $P=0.003$]. We found no differences between CS and reference population in educational achievement, marital status, and parenthood. Among CS patients, female sex, high age, low education, comorbidity, and a history of depression predicted lower likelihood of returning to work. When adjusted for the other factors, adrenal CS patients had better chance of returning to work than pituitary CS.
Conclusion
1) CS negatively affects essential socioeconomic variables even many years before the diagnosis, 2) Risk predictors included female sex, high age, history of depression, and pituitary CS, 3) The data underpin the importance of an early diagnosis and may also have implications for the management of patients receiving pharmacological glucocorticoid treatment.

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AEP616

Prevalence, predictors and outcomes of acute, life-threatening and perioperative complications in cushing's syndrome

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Introduction
Cushing's syndrome is associated with significant chronic and acute complications including acute thromboembolic and cardiovascular events. We aimed to study the prevalence and predictors of acute and perioperative complications in patients with active Cushing's syndrome.

Methods
The prevalence, predictors and outcomes of acute, life-threatening and perioperative complications were evaluated in a cohort of patients with active biochemically verified Cushing's syndrome attending our endocrine department between 1978 and 2016. Any medical complications necessitating hospitalization, including admission to intensive care units (ICUs), from appearance of first symptoms of hypercortisolism until one year after biochemical remission by surgery (or, where surgical remission was not achieved, during continuing follow-up) were recorded and classified. Baseline factors relating to and predicting acute complications were tested using uni- and multivariate analysis.
Results
242 patients (m/f $n=54/188$) with Cushing's syndrome (pituitary $n=99$, adrenal $n=116$, ectopic $n=27$) were included in this study, 14% of which had malignant disease.
55% of patients experienced at least one acute complication including electrolyte disturbances (24%), infections (28%), thromboembolic events (19%: including 4% with cerebrovascular events, 9% with pulmonary embolisms and 6% with other thromboembolic events), cardiac arrhythmias necessitating medical intervention (5%), hypertensive crises (9%) and acute coronary events (3%).
The number of complications per patient significantly correlated with age, duration of hypercortisolism, severity of hypercortisolism (measured by biochemical parameters such as 24-hours urinary free cortisol – UFC), as well as markers of glucose and lipid metabolism. Multiple regression analysis revealed age at diagnosis, fasting glucose and UFC as independent predictors of the number of acute complications per patient. When patients with malignant disease were excluded from analysis, fasting glucose and UFC remained significant predictors. At least one ICU admission (excluding post-surgical observance) was required in 13% of patients. In the whole cohort as well as when malignant cases were excluded, the number of ICU days per patient was significantly related to age at diagnosis, parameters of glucose metabolism, and UFC, with UFC being an independent predictor of the number of ICU days per patient.
Conclusion
This cohort analysis highlights the high prevalence of acute and perioperative complications in Cushing's syndrome, with one in eight patients suffering a life-threatening situation necessitating ICU admission. These acute complications are positively predicted by the duration and degree of hypercortisolism, age and metabolic parameters, emphasizing the necessity for acute interventions aiming to reduce cortisol excess even before definitive disease cure is achieved.

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AEP617

SST5 expression and USP8 mutation in functioning and silent corticotroph pituitary tumors

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Context
Somatostatin receptor type 5 (SST5) is inconsistently expressed by corticotroph tumors, with higher expression found in corticotropinomas having ubiquitin-specific protease 8 (USP8) mutations.
Aims
To study the correlation between characteristics of corticotropinomasand SST5 expression/USP8 mutation status; to describe the response to pasireotide in 5 patients.
Design
Retrospective cohort study.
Methods
Clinico-biochemical, radiological and pathological data of 62 patients, operated for a functioning orsilent corticotropinoma between 2013 and 2017, were collected. SST5 expression was measured by immunohistochemistry (clone UMB-4, Abcam, IRS>1 being considered positive) and Sanger sequencing was performed on 50 tumors to screen for USP8 mutations.
Results
SST5 expression was positive in 26 (41.9%) pituitary tumors. A moderate or strong IRS was found in 25.9% of the cohort and in 37.1% of the functioning corticotropinomas. Among functioning tumors, those expressing SST5 were more frequent in women (91.7% vs 60%; $P=0.004$) and had a lower grade ($P=0.04$) compared to others. USP8 mutations were identified in 26% of the cohort and were more frequent in functioning ($n=11/30$, 36.7%) compared to silent tumors ($n=2/20$, 10%; $P=0.05$). SST5 expression was more frequent in USP8 mut vs USP8wt tumors (90.9% vs 36.8%; $P=0.007$). Among treated patients, normal urinary free cortisol levels were obtained in 3 patients (IRS 0, 2, 6) while a 4.5-fold decrease was observed in one patient (IRS 4).
Conclusion
SST5 expression appears to be associated with functioning, USP8 mutand lower grade corticotropinomas. A correlation between SST5 expression or USP8 mut and response to pasireotide remains to be confirmed.

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AEP618

Efficacy, safety and pitfalls of glucocorticoid therapy for patients with autoimmune hypophysitis

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Background and aim
Autoimmune hypophysitis (AH) is a rare immune-mediated inflammatory disease. Glucocorticoid therapy represents a therapeutic choice for AH patients with symptoms from mass effect, such as headache and optic nerve compression. However, effective methods and adverse events of glucocorticoid therapy are unclear. We aimed to evaluate the efficacy and safety of glucocorticoid therapy in AH patients.
Patients and methods
The subjects were all patients who had been diagnosed as AH and who underwent glucocorticoid therapy at our hospital from January 1, 2013 to December 31, 2018. We performed a retrospective analysis based on the clinical records of these subjects. We investigated the symptoms, endocrine function and treatment complications.
Results
Sixteen patients (median age at diagnosis: 42 years; range, 29–75 years) were included. The initial treatments were; prednisolone ($n=7$) methylprednisolone pulse therapy ($n=8$) and hydrocortisone ($n=1$). The median duration of glucocorticoid treatment was 22 months. The median follow-up was 47.5 months. Headache and visual impairment improved in all patients within 3 months after the initiation of glucocorticoid therapy. Glucocorticoid therapy was effective for achieving mass reduction on MRI in 14 cases (88%). However, four patients relapsed during treatment with physiologic dose of hydrocortisone. Two of these patients underwent biopsy of the enlarged lesion again. In these cases, the diagnosis changed to germinoma and malignant lymphoma, respectively. As for the endocrine function, the change in the number of cases of hypopituitarism after the initiation of glucocorticoid therapy was changed as follows: GH, 12 to 7 cases; PRL, 8 to 2; gonadotropin, 10 to 7; TSH, 10 to 11; ACTH, 9 to 12; ADH, 12 to 11. As for adverse events, the mean BMI significantly increased from 24.6 to 27.0 kg/m^2. Two patients newly developed diabetes mellitus and one patient developed femoral head necrosis. These adverse events appeared in patients who underwent pulse therapy followed by prednisolone.
Discussion
Our study revealed that glucocorticoid therapy contributed to the improvement of symptoms due to mass effect in AH patients but did not improve their endocrine functions. It must be noted that two of recurrent cases were insidious malignant diseases. It is important to carefully reassess the diagnosis and clinical course without blindly believing pathological data. In addition, the combination of steroid pulse therapy and prednisolone caused some complications but also ameliorated diabetes insipidus in one case. Further studies are required to establish the efficacy and safety of glucocorticoid therapy in AH patients.

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AEP619

Observational study of aetiology, efficacy of treatment and outcomes of hyponatraemia following pituitary surgery in a major neurosurgical centre

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Introduction
Hyponatraemia is a relatively common complication following pituitary surgery. However, there is sparse data about its optimal management and impact on clinical outcomes.
Aims
To review the treatment and patient outcomes of hyponatraemia following pituitary surgery.
Methods
A retrospective single-centre study included all inpatients who developed serum sodium (sNa) ≤ 132 mmol/l following pituitary surgery from January 2016 to December 2019.
Results
Amongst 765 patients who underwent pituitary surgery over a 4-year period, 80 (10.4%) developed sNa ≤ 132 mmol/l including 42% males with a median age of 58 years. The commonest type of pituitary lesion was non-functioning pituitary adenoma (53%), followed by Cushing's disease (11%), acromegaly (10%), craniopharyngioma (9%), and prolactinoma (5%). The mean baseline preoperative sNa level was 139 mmol/l. Postoperatively, the mean sNa was 137, 134 and 132 mmol/l on day 3, 5 and 7 respectively. The mean nadir sNa was 126 mmol/l and occurred on average 6.7 days after surgery, with 31 patients (38%) having nadir Na ≤ 125 mmol/l. The proportion of hyponatraemic patients who developed postoperative CSF leak and required lumber drainage was 16.2%, much higher than 5% amongst normonatraemic patients.
The commonest cause of hyponatraemia was SIADH (77.5%), followed by hypocortisolism (6.2%) and overzealous DDAVP administration for diabetes insipidus (6.2%), while no cases of cerebral salt wasting were documented. Treatment was fluid restriction in the majority of patients (80%), ranging from 500–1500 ml/day, while 6 patients (7.5%) were administered hypertonic saline and one patient (1.3%) received tolvaptan.
Post therapy initiation, mean sNa was 128, 129, 129, and 134 mmol/l on day 1, 2, 3 and 5 respectively. The mean time to achieve Na > 5 mmol/l in SIADH group was 4.2 days. The mean Na on discharge was 137 mmol/l, while the readmission rate was 10% and the mean length of hospital stay was 11.5 days.
Conclusion
Hyponatraemia can occur 5–7 days following pituitary surgery, primarily caused by SIADH. Postoperative CSF leak is an independent risk factor for development of hyponatraemia after pituitary surgery.
The effectiveness of fluid restriction was limited, as evidenced by slow Na correction with mean time of 4.2 days to achieve Na > 5 mmol/l, contributing to increased length of hospital stay. This study highlights the need to study the efficacy and safety of agents, such as vaptans and urea, for the management of hyponatraemia after pituitary surgery.

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AEP620

Growth hormone deficiency in childhood acute lymphoblastic leukemia survivors – should systematic stimulation test be performed in all irradiated children?

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Introduction
The combination of chemotherapy with prophylatic cranial radiotherapy (C-RT) allowed the improvement of survival rates of pediatric acute lymphoblastic leukemia (ALL) survivors while putting them at risk of develeping long-term endocrine deficiencies, like growth hormone deficiency (GHD).
Current evidence suggests that the prevalence of GHD in children treated with radiation doses ≥ 30–50 Gy for non-pituitary brain tumors is >50% and 100% in those exposed to the same dose for pituitary brain tumors. However, the prevalence of GHD in the setting of lower doses used for hematological malignancies (18–24 Gy) is not so well characterized.
Our aim was to evaluate our cohort of childhood ALL survivors that developed GHD.
Methods
Retrospective analysis of childhood AAL survivors followed the Late-Effects Clinics of our center between 1980–2019.
Results
We found 324 eligible patients with a mean follow-up of 7.9 ± 6.1 years. The mean age of ALL diagnosis was 6.1 ± 4.1 years. They were all treated with chemotherapy, 235 (72,5%) patients were exposed to C-RT with a median dose of 18 Gy (12–37). Sixty-one (18.8%) patients had hematopoietic cell transplantation, from whom 31 (50%) had total body irradion. We identified 120 cases (37%) of GHD with a mean age at diagnosis of 11,5 ± 4,3 years. Within the 235 irradiated patients of the cohort, we found 113 (49,8%) cases of GHD and this percentage raised to 73.9% when we analysed those who were submitted to insulin-tolerance test (ITT). The mean SDS of IGF-1, stature, growth velocity and bone age at diagnosis were –0.93 ± 1.09, –1.3 ± 1.2, –1.4 ± 1.1 and –0.76 ± 1.5, respectively. Sixty-six of the 120 (55%) patients with GHD were treated with somatropin. From the 50 treated patients in whom was possible to evaluate the final stature, 46 (92%) reached the family target heigh (FTH). This was not true for the non-treated patients with GHD (P = 0,017).
Conclusion
GHD was a common finding in our cohort and C-RT played a major role in its development. Our data show that GHD cases might be underestimated if ITT is not performed since the majority of patients didn´t have a severe IGF-1 deficit nor auxology ≤ 2SDS at diagnosis. We thereby highlight the importance of performing systematic GH stimulation test in irradiated children, given that a timely somatropin reposition allows the achievement of FTH.

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AEP621

9-CIS retinoic acid decreases pomc expression and cell viability in experimental model of ectopic cushing syndrome

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Ectopic Cushing syndrome (EAS) is a rare condition characterized by ACTH-dependent hypercortisolism resistant to normal physiologic suppression by glucocorticoids. EAS is due to an extra-pituitary tumor producing bioactive molecules generated by post-translational cleavage of the proopiomelanocortin gene (POMC). EAS is associated with significant morbidity and mortality and although surgical resection of the primary ACTH-producing tumor remains the mainstay of therapy, not all tumors are easily and rapidly localized or are amenable to complete resection often exacerbating clinical symptoms. In this view pharmacological approach can play a crucial role but a safe and effective therapy is still lacking. Beside inhibitors of adrenal cortisol secretion, somatostatin analogs and dopamine agonists, alone or in combination, have been tried, with acceptable results only in a limited number of patients. 9 cis retinoic acid (RA) is derived from vitamin A showing encouraging effect in regulating ACTH secretion and cortisol levels in patients affected by Cushing's disease. We demonstrated that RA effect in reducing POMC transcription and ACTH production could be potentiated by the co-treatment with Bromocriptine (Br) as a consequence of the permissive role that RA exert on the dopamine receptor type-2 (DRD2). Aim of the present study was to evaluate whether RA alone or in combination with Br is effective in regulating POMC expression and cell viability in cellular model of EAS – i.e. the SCLC-derived cell line DMS79, and primary cultures from 4 bronchopulmonary carcinoids. In DMS79 RA induced a significant dose-dependent decrease in both POMC promotorial activity (67% of control cells at 1 uM, P = 0.0326) and mRNA steady state level (47% at 100 nM, P = 0.0023). After a prolonged incubation (6 days) 1uM RA induce a 39% reduction in cell viability without changes in cell cycle distribution. Concerning DRD2 expression, RA stimulated DRD2 promotorial activity and RNA expression in a dose dependent manner with maximal effect at 1 uM in both assays (130% P = 0.00035, and 424% of control cells, P = 0.00011, respectively). Interestingly, in 3 out 4 tumor cultures, ACTH

secretion was reduced of nearly 30% respect to control cells in presence of the combination of RA (5 nM) and Br (500 nM), while single drugs were less effective. Concluding, the effects of RA on POMC synthesis and cell viability in DMS79, and of the combination RA/Br on ACTH secretion in pulmonary carcinoids may represent a suitable starting point for assessing the potential of this treatment regimen in EAS. and has potentially important implications for novel therapeutic approaches.

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AEP622

Sporadic neuroendocrine neoplasms in young-adult patients: Differences in natural history, prognosis and treatment compared to adult-elderly patients

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Introduction
Sporadic neuroendocrine neoplasms (NEN) occur rarely in young-adult (YA) patients, with an estimated incidence is about 2.8 cases per million, and data specific to their epidemiology are limited. The aim of our study was to better characterize the natural history, prognosis and management of NEN in YA patients (≤35 years old) compared to adult-elderly (AE; >35 years old).
Methods
A retrospective observational study including 204 patients, of which 24 (11.8%) YA and 180 (88.2%) AE, with confirmed diagnosis of sporadic NEN and referred to ENETS Centre of Excellence of Naples – Federico II University between 2010 and 2019 was conducted. Clinical and pathological data, type of treatment, disease-specific survival (DSS) and recurrence-free survival (RFS) were evaluated.
Results
Median age at diagnosis was 25 (16–35) years in YA and 59 (36–84) years in AE patients ($P<0.001$). Female gender was slightly more frequent in YA [M:F=9:15; odds ratio (OR) 1.3, 95% CI 0.9–1.8]. Primary tumor site significantly differed between YA and AE patients ($\chi^2=68.5$, $P<0.001$), being appendix the most common site of origin (41.7% vs 1.1%, respectively), followed by pancreas (33.3% vs 26.7%), lung (16.7% vs 20%) and midgut 4.2% vs 12.2%). Other tumor sites were more frequent in AE compared to YA patients (40.0% vs 4.2%). YA had a significantly higher frequency of low-grade well differentiate (G1) tumors in comparison to AE (78.3% vs 41.3%, OR 1.9, 95% CI 1.4–2.5, $P=0.001$). Functioning tumors were also more frequent in YA patients compared to AE (OR 2.2, 95% CI 0.8-5.4, $P=0.09$), and this was statistically significant considering only the pancreatic NEN (62.5% vs 20.8% in YA and AE, respectively; OR 3.0, 95% CI 1.4-6.5, $P=0.01$). Treatment strategy also differed, being YA treated with fewer regimes (OR 0.4, 95% CI 0.2-0.9, $P=0.007$), including surgery (91.7% vs 70.6%, $\chi^2=4.8$, $P=0.03$) and SSA (25% vs 53.9%, $\chi^2=7.1$, $P=0.008$). Targeted- and chemotherapy were equally used. No differences in DSS and RFS were observed, although YA patients had a trend to a better RFS (median 180 vs 93 months, HR 0.45, $P=0.07$). Among the YA group, age <19 years and G1 tumors were associated with better RFS ($P=0.04$ and $P=0.03$, respectively), although they were not confirmed as prognostic factors at multivariate analysis.
Conclusion
Clinical presentation of NEN significantly differed between YA and AE patients. Due to the lack of prognostic markers, awareness of these rare neoplasms results crucial for a better management.

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AEP623

Temporal trends in incidence, evaluation and management of neuroendocrine neoplasms of the appendix-15 years' experience

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Introduction
Appendiceal neuroendocrine neoplasms (ANEN) account for approximately 50% of all primary tumors of the appendix and are between the first and third-most frequent gastrointestinal neuroendocrine neoplasms. Data regarding trends in incidence, management and prognosis of ANEN is limited.
Aims
To evaluate temporal trends in ANEN incidence, evaluation and management over a 13-year period.
Materials and Methods
Appendectomy pathology reports from a single tertiary center were reviewed. Epidemiological, clinical and pathological data of ANEN patients were collected from electronic patient files.
Results
Between January 2005 and December 2018, 8,327 appendectomies were performed. A total of 57 ANENs were diagnosed. Theirmean age was 31.7±49 years; 70.2% were females; 17.5% were of Arab ethnicity; and 22.8% werediagnosed under 18 years of age.
The cohort was subdivided according to year of diagnosis into Period A (2005–2011) and Period B (2012–2018). No differences were found in ANEN incidence (Period A 0.68% and Period B 0.62%, respectively, $P=0.104$) or epidemiologic characteristics between periods. Pathologic features were similar in the two subgroups, although pathology reports were more comprehensive and applicable to international guidelines in Period B. More patients in Period B were followed in dedicated clinics. Somatostatin receptor imaging and biochemical studies such as serum Chromogranin A and urinary 5-Hidroxy-indol-acetic -acid (5-HIAA) was also more frequently used in Period B. Fifteen patients underwent right hemicolectomy (8/31 in period A, 7/26 in period B, $P=0.925$). Pathologic features of ANEN were similar between the two subgroups. Residual disease in hemicolectomy specimen was observed in 2/7 patients in Period A and 3/6 patients in Period B. For the duration of follow up (10.8±1.7 years in Period A and 3.5±1.9 years in Period B, $P<0.001$) all patients remained alive, and all patients except one remained disease free.
Conclusions
Over a 13-year period, no distinct temporal changes in epidemiological, clinical or pathological features of ANENs were noted. Although after 2011 the clinico-pathological evaluation was more detailed and elaborated, there was no change in hemicolectomy rate or disease prognosis. Large scale studies are needed, in order to consider revision of current international guidelines for ANEN evaluation and treatment, in particular the necessity of right hemicolectomy.

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AEP624

Contribution of NGS in the genetic analysis of neuroendocrine tumors associated with Multiple Endocrine neoplasia type 1 (MEN 1)

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Objective
Next Generation Sequencing technique (NGS) allows the analysis of a whole set of genes in the same time. It is, now, used, in our laboratory for the genetic screening of neuroendocrine tumors associated with Multiple Endocrine neoplasia type 1(MEN1)The objective of the present study was to assess the efficiency of this approach and the relevance of the results regarding the current genetic screening recommendations.
Methods
The data of all patients tested by NGS during the last 3 years forneuroendocrine tumors associated with MEN1 were collected. NGS technique allowed the analysis of the coding sequence and the intronic bounds of 13 genes in a total of 583 patients.
Results
Genetic variants were identified in 53 patients: 30 of them were located in the MEN 1 gene, 5 in CDKN1B et 6 in a gene involved in familial hypocalciuric hypercalcema 38 were classified as pathogenic or probably pathogenic variants and 15 were classified as variant of undetermined signification. Most of patients with more than one neuroendocrine tumor did not carry any mutation. Statistical analysis identified three main predictors of positive genetic testing: male gender, age less than 50 years old at diagnosis, and having more than one type of endocrine tumor.
Conclusion
In this study, a genetic variant has been identified by NGS in 10% of cases with predictive factors of positive genetic testing in accordance with current guidelines. This suggests that NGS approach is a reliable technique for the

genetic screening of patients with neuroendocrine tumors. However, other approaches remain necessary to identify more mutations. Variants interpretation remains a major problem which needs a close collaboration between laboratories and clinicians and the improvement of new effective tools.

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AEP625

Malignant insulinoma treated with ^{177}Lu-DOTATATE: Results in the first year post-therapy

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Introduction

Neuroendocrine tumors (NETs) are rare and their clinical behavior and prognosis correlates with mitotic rate and Ki-67 index. Most patients with advanced NET have liver metastases unresectable and somatostatin analogues are the initial therapy of choice but when disease progresses despite treatment and there are positive somatostatin receptors, peptide receptor radioligand therapy (PRRT), using lutetium-177, is a therapeutic option.

Clinical case

A 42-year-old male with episodes of fasting hypoglycemia was diagnosed with a well-differentiated low-grade NET G1 Insulin secretor, located in the pancreas body, with multiple liver metastases, after performing a 72-hour fasting test, abdominal magnetic resonance (MR) and fine needle aspiration by echoendoscopy. Biochemical data to highlight: chromogranin 592 ng/ml (≤ 100), gastrin 409 pg/ml (13–115), GOT 77 IU/l, GPT 87 IU/l, GGT 170 IU/l. Abdominal MR revealed multiple focal lesions distributed throughout the hepatic parenchyma, 5–30 mm in size and 2.5 × 1.7 cm pancreatic mass located in the distal body. 111-In-pentetreotide SPECT-CT showed multiple deposits of intense uptake and variable size in hepatic parenchyma with high expression of somatostatin receptors (SSTRs) and small deposit of discrete uptake in the pancreas body. Hypoglycemia, not controlled with diazoxide, disappeared with sandostatin LAR. Distal spleno-pancreatectomy was performed in June 2017 and the histological report confirmed a pancreatic NET G1 with numerous perineural infiltrations and vascular embolisms, free circumferential borders, and metastases in 4 of 21 isolated nodes. Post-surgery markers: chromogranin 737.4 ng/ml, gastrin >1,000 pg/ml. In SPECT-CT there were no significant changes in liver metastases, so PRRT with 177Lu-DOTATATE combined with Sandostatin LAR 30 mg IM/month was scheduled. Temozolomide-capecitabine chemotherapy was administered prior to 4 lutetium cycles initiated in June 2018 and completed in January 2019. After 2 cycles, chromogranin was 108.9 ng/ml and gastrin 32 pg/ml. The markers are negative since February 2019 and liver function progressively improved. Since October 2018, successive CT scans report a decrease in the size and uptake of hepatic focal lesions with an increase in central necrosis compatible with a partial response to treatment, and pentetreotide scintigraphy in March 2019 demonstrates a significant improvement in liver involvement.

Discussion

Pancreatic NETs are more aggressive but respond better to systemic agents. The benefit of conventional chemotherapy in malignant insulinoma is limited and PRRT with lutetium-177 have proven its efficacy and low toxicity so could be a suitable systemic therapy in selected patients.

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AEP626

Surgical and survival outcomes of early peptide receptor radionuclide therapy for downstaging locally advanced or oligometastatic pancreatic neuroendocrine neoplasms

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Introduction

Pancreatic neuroendocrine neoplasm (pNEN) patients often present with locally advanced or metastatic disease. The objective response rate of peptide receptor radionuclide therapy (PRRT) in pNENs is 55%. Therefore, PRRT may be a possibility for patients who are not eligible for upfront curative surgery.

Aims

To assess the potency of PRRT to render locally advanced or oligometastatic pNENs resectable and to evaluate the effect of surgery after early PRRT on survival.

Material and methods

A single-center retrospective analysis was performed on 50 pNEN patients, treated between 2000 and 2019 with ^{177}Lu-DOTATATE with a neoadjuvant or downstaging intent. Patients had resectable, borderline resectable or unresectable locoregional disease and/or metastatic disease.

Results

After PRRT, 26 patients underwent surgery with curative intent. Surgical and non-surgical patients had equal tumor diameters and metastatic sites at baseline. Patients in the surgical group had more grade 1 tumors than those in the non-surgical group ($P=0.001$) and more often completed the intended PRRT dose of 29.6 GBq ($P=0.007$). In 54% and 46% of the surgical and in 21% and 63% of the non-surgical patients, best responses were partial response and stable disease, respectively ($P=0.02$). One patient died due to surgical complications. Median progression free survival was 28 months for the non-surgical group and 68 months for the surgical group ($P=0.009$). Median overall survival was 66 months for the non-surgical group compared to 177 months for the surgical group ($P=0.002$).

Conclusions

This study shows the favorable long-term outcomes of pNEN patients that underwent surgery after neoadjuvant PRRT. Early PRRT followed by surgical evaluation is an option for patients with unresectable or oligometastatic pNEN.

Keywords: neoadjuvant, peptide receptor radionuclide therapy, neuroendocrine, pancreas, surgery.

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AEP627

Absolute oral bioavailability and absorption, metabolism, excretion of [14C]-Labeled paltusotine (CRN00808), an orally bioavailable, nonpeptide, selective, somatostatin receptor 2 (sst2) biased agonist for the treatment of acromegaly

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Injected depot formulations of somatostatin peptide analogs are routinely used to treat acromegaly and neuroendocrine tumors (NETs). Paltusotine (CRN00808), a small molecule nonpeptide selective somatostatin receptor 2 (sst2) agonist, is being evaluated for efficacy and safety in patients with acromegaly. The current Phase 1 study (NCT04246749) was conducted in two Parts: In Part A, the absorption, metabolism, excretion, and mass balance of a single oral dose of 20 mg [14C]-paltusotine (3.0 MBq) oral solution was characterized in six healthy male subjects. Plasma, blood, urine, and feces were collected for up to 432 hours, and were analyzed for total radioactivity and paltusotine concentrations (plasma only). Metabolite profiling was conducted on the plasma, urine, and feces samples. In Part B, the absolute bioavailability of paltusotine was determined by administering a single oral dose of 20 mg paltusotine compared with a single micro-tracer intravenous (IV) bolus injection of 0.050 mg [14C]-paltusotine (0.0185 MBq) in five healthy male subjects. The IV dose was administered approximately 90 minutes after the oral dose. Plasma samples were collected for up to 144 hours and were analyzed for paltusotine and [14C]-paltusotine concentrations.

Part A of the study show that >90% of radioactivity was recovered within 7 days of dosing. The primary route of excretion was the feces (89.9% of dose) with minimal excretion in the urine (3.9% of dose). Absorption of total [14C]-paltusotine-derived radioactivity in plasma was rapid (median Tmax = 1 hour), and the geometric mean of Cmax, AUC0-inf, and t1/2 were determined to be 189 ng-equivalents/ml, 3180 ng-equivalents.hr/ml, and 31 hours, respectively. The pharmacokinetic parameters of unchanged paltusotine in plasma were similar, suggesting that majority of the circulating drug-derived radioactivity is accounted for by unchanged paltusotine and there are no abundant circulating metabolites. Data from Part B of the study show that the mean oral bioavailability of paltusotine was 70% and the mean clearance and volume of distribution after IV administration were 5.3 l/h and 240 l, respectively. Treatment emergent adverse events associated with paltusotine were generally mild and transient, and consistent with those reported with other somatostatin agonists. In conclusion, results from this clinical trial in healthy volunteers confirm that paltusotine has excellent drug-like properties for chronic once-daily oral treatment of patients with acromegaly and NETs.

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AEP628

Safety and IGF-1 levels with once daily oral sst2 agonist paltusotine (CRN00808) in acromegaly patients previously treated with peptide long-acting somatostatin receptor ligands: Initial data from the open label ACROBAT Edge phase 2 study

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Peptide long-acting somatostatin receptor ligands (SRLs) are a first line medical treatment for acromegaly but are not efficiently absorbed when delivered orally. Years of injections with SRLs are associated with variable dose delivery, injection site reactions, and excessive life burden. Paltusotine (CRN00808) is a nonpeptide small molecule somatostatin type 2 (sst2) receptor agonist with high oral bioavailability (70%) and a 42–50 hour terminal elimination half-life in healthy volunteers, suitable for once daily dosing. We hypothesized that patients partially controlled on stable long-acting SRLs could successfully switch to once daily oral paltusotine while maintaining baseline IGF-1 levels. ACROBAT Edge (NCT03789656) is an ongoing open label, single-arm exploratory study to evaluate the safety and efficacy of paltusotine in patients with acromegaly who have not achieved normal IGF-1 levels with SRL monotherapy (group 1) or with a SRL in combination with a dopamine agonist (group 2). Additional exploratory subgroups, also eligible for enrollment in this trial, all have normal IGF-1 at baseline and include subjects treated with a SRL in combination with a dopamine agonist (group 3), pasireotide LAR monotherapy (group 4), or a SRL in combination with pegvisomant (group 5). The study schedule requires a final SRL injection to be administered 4 weeks prior to switching to paltusotine monotherapy for 13 weeks of dose titration, followed by a 4-week drug washout period. Change from baseline in IGF-1 to the completion of the 13-week dose titration period is the primary endpoint to be evaluated in a target sample size of 30 subjects in groups 1 and 2. The rise in IGF-1 during the wash out period is used to provide supportive evidence of efficacy. The IDS-iSYS assay calibrated to WHO recombinant reference standard 02/254 is used to measure IGF-1. Initial data available from the ACROBAT Edge study will be reported. This will include summary statistics for IGF-1 at baseline, completion of treatment period, and after washout. Safety data will also be summarized. To date, there have been no reported serious adverse events or treatment discontinuations due to adverse events. This data snapshot of open label data from ACROBAT Edge will provide important information in guiding clinical development of paltusotine for the treatment of acromegaly.

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AEP629

The time, mode and markers of pituitary function deterioration in patients with PROP1 mutation. Single centre, longitudinal observation

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Introduction
The mode of pituitary function deterioration in patients with PROP1 mutation is not fully known and understood. The function of adrenal axis requires special attention.
Aim
To investigate the time/mode/markers of pituitary function deterioration in families/sporadic patients with PROP1 mutation during longitudinal observation.
Methods
We performed retrospective longitudinal (36.4 years, s.d. = 13.6) analysis of 28 patients (23 with complete data, 11 M/12 W) with PROP1 mutation, including 7 families (16/23 70% of investigated population; 20/28 overall), with 2–4 affected siblings who were under medical supervision of the paediatric/adult endocrinology departments of our university. Follow up investigation of adrenal axis insufficiency (AI) with repeated ACTH analogue (Synacthen) and CRH tests were performed in 21 and 7 patients, respectively.
Results
All patients initially presented with growth failure at mean age (MA) 7.0 years (s.d. = 3.7). 14/23 patients were first diagnosed with GH/TSH deficiency occurred simultaneously, MA 6.6 years (s.d. = 3.0). 13/28 (older patients) received no/delayed/intermittent GH treatment in childhood. Gonadal deficiency was diagnosed in all patients MA 16.0 years (s.d. = 4.85). 19/23 (82,6%) of patients developed adrenal deficiency MA 25 years (s.d. = 16.0), the oldest newly diagnosed at the age of 57. The actual average dose of HC supplementation is 17.8 mg/day (0.25 mg/kg). There were no specific mode/order of pituitary deterioration among siblings. Mean morning cortisol and ACTH in patients with AI were 5.7 (s.d. = 4.0) and 20.7 (s.d. = 7.7) vs without AI 11.8 (s.d. = 5.5) and 21.8 (s.d. = 8.1), respectively. The peak cortisol increase during Synacthen test was in 60' by 3.2 (s.d. = 0,83) and by 1.9 times (s.d. = 0,26) in patients with/without AI, respectively. In CRH test the peak values of cortisol (in 60–120') and ACTH (in 15–30') were observed accordingly in patients with AI by 3.3 (s.d. = 1.0) and by 3.4 times (s.d. = 0.4) vs patient without AI by 2.5 and by 4.3 times).
Conclusions
In patients with PROP1 mutation there is no specific order of pituitary function deterioration even among affected siblings. Careful monitoring for possible adrenal insufficiency regardless of the time of observation and previous stimulation test results should be carried on. Morning (low) cortisol and ACTH (normal range) cannot serve as a marker of adrenal axis function. The increase of ACTH during CRH test in patients with adrenal insufficiency suggests that corticotropes are responsive. Further studies are needed to better understand the process, to improve the standards of care/diagnostic timing/procedures.

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AEP630

Clinical presentations of patients with MEN 1 syndrome and its phenocopies

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Introduction
Multiple endocrine neoplasia type 1 (MEN 1) is a rare, autosomal dominant disease caused by mutations in the *MEN1* gene. The syndrome predisposes an individual to the development of primary hyperparathyroidism (PHPT), gastroenteropancreatic neuroendocrine tumors (GEP-NETs), pituitary adenomas (PA), as well as other endocrine and non-endocrine tumors

that usually manifest at a young age. If a patient with the MEN 1 phenotype does not carry mutations in the *MEN1* gene, the condition is considered a phenocopy of this syndrome. Comparison of clinical characteristics of mutation-positive and mutation-negative patients may help to identify factors predictive of a positive or negative genetic test.
Materials and methods
The clinical presentations of 85 patients with multiple endocrine neoplasia were analyzed over 5 years. Screening for *MEN1* gene mutations was done by Sanger sequencing or by next-generation sequencing using a panel of genes including *MEN1*.
Results
42 patients carried *MEN1* mutations and 43 patients were mutation-negative. The median age in the phenocopy group was 61 years [48; 65]; in MEN 1 group — 38 years [32; 50] with a predominance of females over males in both groups (82% in non-carriers vs 71% in carriers). The most common combination in the phenocopy group was PA/PHPT (91%) and acromegaly among these patients appeared in 72% cases (versus 11% in *MEN1* carriers). In *MEN1* mutation carriers the most frequent combination was PHPT/GEP-NETs/PA (57%) and mostly PA secreted prolactin (38%). GEP-NETs developed more frequently in *MEN1*carriers compared to non-carriers (72% and 16%, respectively, $P<0{,}01$). The prevalence of PHPT in both groups was almost 100% and multiple lesions of parathyroid glands were more common in carriers. Adrenal tumors were equally common in both groups (23% in non-carriers and 26% in carriers).
Conclusion
GEP-NETs in patients with MEN1 phenotypes could possibly predict the presence of a *MEN1* mutation. Phenocopies of MEN 1 are quite common and usually occur in older patients, with a female predominance; the most common combination of tumors in this group is PHPT/PA (GH secreting). The etiology of the combination of several endocrine MEN 1-associated tumors in such patients remains unknown. As possible causes, mutations in other, not yet established, genes, epigenetic changes, as well as a random combination of several tumors in one patient can be considered.

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AEP631

Functional panhypopituitarism of anorexia

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A 30-year-old male was admitted to the neurotraumatology ward after head trauma with cerebral concussion, subdural & subarachnoidal haemorrhage. The Endocrinologist was called to evaluate high urinary debits. The patient was healthy until 4 years before admission. He enrolled on variate patterns of alimentary restriction that resulted in the loss of 28 kg. Since then he had visited multiple doctors (Cardiology, Haemathology, Psychiatry, Gastroenterology, Urology, Endocrinology) and performed extensive exams. In conclusion, he had history of sinus bradycardia, normocytic normochromic anemia, bile stones, suspected obstructive incontinence, diabetes insipidus, central hypothyroidism and hypogonadism of unspecified aetiology (normal anterior and posterior pituitary on RMI). From all prescribed drugs he adhered only to levothyroxine 112 mg and testosterone. He complained of weakness, fatigue, nocturia and lack of drive. After a thorough investigation during hospitalization a pathological cause for the syncopal head trauma could not be identified and the history of skipping meals became consistent. Blood tests revealed slight pancytopenia, low testosterone, low IGF-1, normal prolactin, cortisol 12 mg/dl (21 mg/dl after Synacthen), normal FT4 and low FT3, 24 h urinary debits of 2.8–3.6 l of urine with 621 mOsm, normal natremia and blood osmolality. He was discharged weighting 68 kg (192 cm, BMI 18 kg/m^2). Levothyroxine and testosterone were maintained. Control RMI showed a normal pituitary with adequate neural hyperintense sign, anti-hypophyseal Ab were negative. By exclusion and given specially the persistent low IGF-1 and FT3, it was postulated that he had hypopituitarism and possibly mild diabetes insipidus in the context of the alimentary disorder and that the syncope was due to low caloric intake. He was followed up by Nutrition, Psychology, Psychiatry, Physiotherapy and Neurology. Testosterone was weaned off progressively based on symptoms and blood tests and levothyroxine was reduced according to FT3 recovery. After 8 months, CBC was normal, FT3 improved slightly and TT was withing RR. After 12 months, there was increased frequency of shaving and body hair density, he recovered spontaneous erections and testosterone was stopped. Levothyroxine has been reduced to 88 mg.
Conclusions
Severe caloric restriction results in typical hypopituitarism with preserved ACTH-cortisol axis and less commonly accompanying mild DI. Pharmacological resistance to hormonal substitution is well known, caloric intake is the mainstay of treatment for adequate functional recovery.

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AEP632

A case of primary hypophysitis with cavernous sinus infiltration causing an unilateral internal carotid artery occlusion

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Primary hypophysitis (PH) is a rare clinical entity usually presenting with headaches, pituitary deficiency, visual field defects and exceptionally with symptoms of cavernous sinus infiltration such as cranial nerve palsies. An internal carotid artery (ICA) occlusion is unusual complication of PH infiltrating the cavernous sinus. A 32-year old woman presented with a 4-year history of recurring headaches, right retro-orbital pain, periodic diplopia and secondary adrenal insufficiency. She was admitted to the Department of Endocrinology due to deteriorating headaches, right retro-orbital pain, symptoms of the rightsixthcranial nerve palsy and secondary amenorrhea. Hormonal test results revealed panhypopituitarism. MRI scan showeda sellar and suprasellar mass infiltrating the right cavernous sinus. Additionally, a complete occlusion of right ICA was visible which was confirmed by CT-angiography. No other neurological symptoms were present. Based on clinical presentation, results of hormonal tests and MRI the diagnosis of PH was established. High-dose glucocorticosteroids (GCs) treatment was initiated, which resulted in the headaches and retro-orbital pain remission, abducens nerve palsy subsiding and return of regular menses. The patient has been treated for 10 months with a gradual reduction of GCs dose. A partial regression of parasellar infiltration was revealed on MRI scans but ICA occlusion seems to be permanent. Experience in treatment of PH with ICA occlusion is sparse. Similarly, to a few cases published in the literature, in our patient GCs therapy was not successful in restoring blood flow inthe affected ICA, although it improved pituitary function and reduced cranial nerve palsy and headaches.

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ACTH-secreting pituitary tumor with delayed aggressive clinical recurrence – management challenges

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Background
Pituitary adenomas (PA) are slow-growing, benign intracranial tumors. Rarely, they can be histologically and clinically aggressive.
Aim
To present a case of corticotroph PA with aggressive behavior following a long indolent interval after the initial surgery.
Case presentation
A 47 years old female presented in Nov 2007 with right temporal hemianopsia and left eye blindness, associating type 2 DM and severe mixed dyslipidemia. MRI demonstrated a 22×20×25 mm sellar tumor with suprasellar extension. Vision improved significantly following transsphenoidal resection. The patient was lost to follow-up for 12 years, during which she was symptom-free, despite persistence of a significant tumor remnant (21×19×16 mm, MRI in 2011). In Mar 2019, the 59 years old patient returned to our unit, with bitemporal hemianopsia and decreased visual acuity, insulin-requiring DM and dyslipidemia, central obesity, without other signs of Cushing's syndrome. 0800 h cortisolemia (21.13 mg/dl) was unsuppressed by 1 mg o/n DEX (5.85 mg/dl) and LDDST (3.39 mg/dl) and 0800 h ACTH was 26 pg/ml. The patient had thyrotroph, gonadotrop and likely somatotroph insufficiency. A partial transsphenoidal resection of a fibrous, difficult-to-resect tumour, led to biochemical remission of Cushing's disease (CD) (0800 h cortisolemia=5.2 mg/dl and 0.66 mg/dl after 1 mg o/n DEX) but no visual improvement. Post-operative MRI revealed

a 25×18×30 mm tumor with bilateral cavernous sinus invasion and chiasmal compression. A third transsphenoidal resection improved visual fields and acuity significantly and the patient developed corticotroph insufficiency (8AM cortisolemia = 1.46 mg/dl, ACTH = 6.6 pg/ml). Histopathological examination revealed a PA with frequent mitoses, IHC positivity for ACTH only, Ki-67 index 15% and p53 nuclear labeling in 30% of cells. SSTR2 and SSTR5 tumor immunoreactivity was positive, but pasireotide could not be administered for regulatory reasons. Visual fields and acuity declined progressively over 3 months and MRI in Jan 2020 revealed rapid tumor growth (27/30/33 mm). MDT recommendations were for repeat surgery (pending) followed by radiotherapy +/– temozolomide and close follow-up.
Conclusion
We report a case of aggressive functioning corticotroph adenoma occurring after a twelve years indolent interval. Immunohistochemical markers of proliferation predict an unfavourable clinic course and need of multimodal aggressive management. Combined temozolomide and radiotherapy (Stupp protocol) is a possibility.

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Unusual case of women suffering from aggressive silent thyrotropinoma treated with somatostatin analogues during pregnancy

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Background
Thyroid-stimulating hormone (TSH) expressing tumors are one of the rarest pituitary adenomas and comprises 0.5–2% of all cases. To our knowledge, only four cases of thyrotropinoma in a pregnant women have been reported up to date.
Case presentation
We present a case of 24-year old women who reported to gynecologist due to secondary amenorrhea and severe headaches. Commissioned laboratory test showed, among others, prolactin 31.0 ng/ml and TSH 3.5 mIU/l. She was referred for magnetic resonance imaging (MRI) of the pituitary gland, where macroadenoma infiltrating the cavernous sinus was found. The octreoscan showed high expression of somatostatin receptors. The patient underwent incomplete transsphenoidal surgery without complications, what resulted in relief of headaches. Immunohistochemical examination revealed expression of TSH and growth hormone (GH), however, the patient did not had any signs of either secondary hyperthyroidism or GH excess. Therefore, the patient was administered somatostatin analogues, thereby obtaining restoration of regular menstruations. Shortly afterwards the patient became pregnant and the pharmacological treatment was discontinued. In the 11th week of pregnancy a severe headache, impaired vision and drooping of eyelid appeared. Urgent MRI proved large progression of the tumor and she was given short-acting octreotide 100 µg three times daily subcutaneously. As a consequence, rapid improvement and withdrawal of symptoms was observed. In the following weeks of pregnancy the treatment was maintained. Patient was regularly monitored, however, remained asymptomatic. At 30th week of pregnancy she was diagnosed with intrahepatic cholestasis and, therefore, the dose of octreotide was reduced to 100 µg per day and the ursodeoxycholic acid was added. Despite this, in the following weeks of pregnancy no clinical signs of tumor were observed. In 38th week of pregnancy the patient gave birth to a healthy daughter weighting 3800 g. After the pregnancy, she returned to long-acting somatostatin analogues and was qualified for the transsphenoidal surgery with subsequent radiotherapy.
Conclusions
Management of pregnant women with pituitary tumors is complex and requires an individual, patient-centered approach. This should include careful monitoring and calculation of both, maternal and fetal risk-benefit ratio. In the described patient, treatment with somatostatin analogues contributed to the reduction of the tumor size, restoration of the normal function of pituitary gland and, above all, successful conception. Moreover, it allowed the avoidance of surgery during pregnancy and achievement of satisfactory disease control so the patient could gave birth full-term.

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AEP635

Secondary amenorrhea, acute hydrocephalus and syndrome of inappropriate secretion of antidiuretic hormone as first manifestations of neurosarcoidosis

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Introduction
Sarcoidosis affects both the central and peripheral nervous system in 5–16% of patients. In most cases, such involvement occurs within a multi-systemic disease. Endocrine manifestations of neurosarcoidosis can be expressed by hypothalamic dysfunction, diabetes insipidus, hypopituitarism, hyperprolactinemia, in isolated fashion or variedly combined.
Herein, we report a case of neurosarcoidosis revealed by an obstructive hydrocephalus, a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and a secondary amenorrhea in a 34-year-old woman.
Observation
A 34-year-old woman was referred to our department of endocrinology for secondary amenorrheafor the last two years. Her past medical history included an acute obstructive hydrocephalus treated with ventricular drainage and a severe hyponatremia secondary to a SIADH. She reported a weight gain, walking disorders and memory troubles. On physical examination, she had a body weight of 130 kg, a body mass index of 42 kg/m^2 and a blood pressure of 120/70 mmHg. On biological investigations she had a fasting blood glucose of 0.84 g/l, a natremia of 128 mmol/l, a kaliemia of 4.4 mmol/l, a serum osmotic pressure of 254 mOsm/l, a calcemia of 93 mg/l, an urine osmolality of 565 mOsm/kg and an urinary sodium level of 206 mmol/l. On hormonal investigations, she had a TSH of 1.7 mUl/l, a FT4 of 0.97 ng/dl, a morning cortisol of 16.6 µg/dl, a prolactin of 7 µg/l, a FSH of 1.3 IU/l, a LH of 0.45 IU/l and an estradiol of 13 ng/l. The diagnosis of hypogonadotropic hypogonadism was made. The bone densitometry revealed osteoporosis. The cerebro-medullary magnetic resonance imaging showed a micronodular enhancement of the acqueduct, the fornix columns with extension to the 3rd ventricle, the infundibulum, the pituitary stalk and the optic chiasm, as well as the right temporal and right cerebral peduncle associated with micronodular enhancement of the meninges, the base cisterns and perimedullary. The diagnosis of neurosarcoidosis was established. The patient was put on normal sodium diet, water restriction, bisphosphonates and estroprogestative replacement therapy. Then, she was referred to the department of internal medicine.
Discussion and conclusion
Hypothalamo-pituitary involvement by sarcoidosis is a rare condition. Its most frequent disorders are diabetes insipidus and hyperprolactinemia. Recent studies have demonstrated that gonadotropin deficiency was the most frequent manifestation of the disease as in our case. However, the SIADH is not common in neurosarcoidosis. It could be induced by the hydrocephalus. As hyponatremia persisted after ventricular drainage, SIADH might be caused by neurosarcoidosis.

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Complicated endocrinopathy after liver transplantation for unusual diagnosis

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Introduction
Langerhans cell histiocytosis (LCH) is a very rare haematological disease, with difficult diagnosis for its very variable clinical picture. It is caused by monoclonal proliferation of cutaneous Langerhans cells. It affects most commonly the skin and bones, less often bone marrow, liver, pituitary and CNS.
Case report
A 74-year-old female patient with progressive sclerosing cholangitis was referred to a transplant centre to consider liver transplant treatment options.

Langerhans cell histiocytosis (LCH) was diagnosed by a liver biopsy. Other examinations, including trepanobiopsy and PET/CT, revealed no other lesions of LCH. The finding was evaluated by the hematologist as unifocal histiocytosis with isolated liver involvement at MGUS level. After the examination, the patient underwent liver transplantation. Immunosuppressive therapy (tacrolimus, mycophenolate mofetil and corticoids) was initiated. Postoperative course was significantly complicated by bleeding and biliary leak, requiring repeated surgical revisions, protracted abdominal infection and repeated need for percutaneous biloma drainage. Chronic sepsis, malnutrition, sarcopenia, decreased mobility and depressive syndrome dominated in the clinical picture. Two months after transplantation, polyuria (of about 7 – 10 litres/24 hours) appeared. The fluid withdrawal test confirmed suspected diabetes insipidus. Etiopathogenetically, there was a possible association with the administration of linezolid in antibiotic therapy, but also with the underlying histiocytosis. After the application of desmopressin (in doses of 60 – 300 µg/day) the polyuria gradually decreased to diuresis about 3 litres/24 h. CT examination described a small pituitary bearing, possible granuloma in histiocytosis or adenoma. Later, the MR region of the Turkish saddle was performed showing a very small pituitary volume with an empty-sella and slight infundibulum enlargement indicating possible discrete LCH in this region. Pituitary profile revealed hyperprolactinaemia (1912 mIU/l), low levels of LH, FSH and TSH, and normal levels of ACTH as well as cortisol. Cabergoline was added to the therapy. Its administration in a small dose (0.5 mg/week) led to a rapid decrease of prolactinemia. The gradual withdrawal of desmopressin did not cause polyuria to return. Currently, the patient is in a satisfactory clinical condition and except cabergoline treated only with a small dose of corticoids as a part of her maintenance immunosuppressive regiment.
Conclusion
We point to a rare hematological disease complicated with probably related endocrinopathy.

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A rare association of hypogonadotropic hypogonadism and GH deficiency in a patient with Addison's disease

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Introduction
Primary adrenal insufficiency is a classically rare but potentially serious disease due to the risk of acute adrenal crisis. Although autoimmune origin is the first etiology in adults, genetic causes are most common in children. Herein, we reporta case of coexisting hypogonadotropic hypogonadism and growth hormone (GH) deficiency in a patient with Addison's disease.
Observation
A 15-year-old boy was referred to our department for short stature. He had no family history of autoimmune diseases. His past medical history included a primary adrenal insufficiency. This diagnosis was established on the basis of a very low morning cortisol level of 5 nmol/l with a very high ACTH level of 419 ng/l (nr: <48 ng/l). Thus, the patient was put on replacement therapy with hydrocortisone and fludrocortisone.
On physical examination, he had a body height of 146 cm (between –2 S.D. and –3 S.D.) and an impuberism with a Tanner classification of G1A1P1. His bone age was less than 10 years. The peak of GH under insulin induced hypoglycemia test was 1 mU/l and under glucagon test 3.6 mU/l. A complete deficit in GH has been established. The evaluation of the other pituitary axes revealed hypogonadotropichypogonadism with absence of response to the GnRH test. Thyroid function (TSH and FT4) and prolactinemia were normal. The hypothalamic-pituitary MRI revealed a partial empty sella. The patient received treatment with growth hormone (at a dose of 0.02 mg/kg/day) for 2 years. The final height was 160 cm. He was also put on androgens with a normal development of secondary sexual characteristics.
Conclusion
We report an unusual coexisting of hypogonadotropic hypogonadism, GH deficiency and Addison's disease. The autoimmune involvement of adrenal gland and pituitary is unlikely in our patient since his thyrotropic and corticotropic axes were not affected. A genetic mutation affecting both the adrenal gland and the pituitary gland should be evoked, in particular the DAX1 mutation. This mutation results in adrenal hypoplasia and hypogonadotropichypogonadism. Its role in the development of GH deficiency is not known but it has been described in the literature in particular with a novel missense NROB1 mutation.

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46XY DSD as initial clinical presentation in a patient with syndromic combined pituitary hormones deficiency

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Background
Combined pituitary hormone deficiency (CPHD) is characterized by multiple pituitary hormone deficiencies, due to mutations of pituitary transcription factors involved in pituitary ontogenesis. The genetic basis for CPHD is complex, involving a variety of syndromic and non-syndromic presentations with variable degrees of phenotype-genotype correlations. In male infants with CPHD, gonadotropin deficiency is suggested by the presence of a microphallus and undescended testes, as the growth of the penis and normal testicular descent are dependent upon the normal secretion of fetal LH in the second and the third trimesters. However, more severe genital abnormalities, such as hypospadias or ambiguous genitalia, indicate a defect of hCG-driven androgen secretion and/or action in early fetal life, before the initiation of endogenous hypothalamic-pituitary-gonadal axis activity. Herein, we describe a clinical case of a 15-year-old and 5 months male with a history of premature delivery, ambiguous genitalia at birth (Prader stage 3), who was admitted to the Department of Endocrinology due to underdeveloped genitalia and delayed puberty. Postnatally, it was suspected apartial 46XYDSD after chromosome analysis. Physical examination revealed an overweight patient of normal height, Taner stage 1, micropenis, bifid scrotum, penoscrotal hypospadias, palpable prepubertal gonads in the scrotum (after orchidopexy). Hormonal assayse stablished the combined deficiencies of pituitary hormones: GH, TSH, ACTH, and gonadotropins. The provocative tests revealed no response to GnRH but a significant increase in testosterone level after hCG. Ultrasound imaging didn't find either Mullerian structures or adrenal hyperplasia; the testicular structure was normal, but with a hypoplasic aspect. Brain MRI showed a normal adenohypophysis, a hypoplasic and ectopic neurohypophysis, and a thin pituitary stalk with interruptions. The hand radiogram revealed a bone age of 12. The genetic testing results are at work.
Conclusion
This case illustrates an atypical presentation of CPDH with normal growth despite GH deficiency and genital anomalies indicating an androgen deficiency in early fetal life. It also highlights the need to evaluate the hypothalamic-pituitary axis in selected cases of intersex, and questions the prevailing assumptionsabout the mechanisms underlying the control of testosterone secretion during embryogenesis.

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Clinical and hormonal features of congenital hypopituitarism

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Introduction
Congenital hypopituitarism is a rare disease induced by mutations in transcription factors involved in the pituitary development or ubiquitous transcription factors. It can be associated with a malformative syndrome. We herein describe clinical and hormonal features of congenital hypopituitarism in two Tunisian families.
Observation 1
We report the case of three sisters, born at term to healthy consanguineous parents. The index case was referred at the age of 20 years for delayed

growth. Physical examination showed a short stature with a height of 125 cm (< −4 s.d.), an immature appearance, a high-arched palate, low blood pressure and female external genital organs with Tanner stage 1. Her bone age was seven years. On hormonal investigations, she had a combined pituitary hormone deficiency. The pituitary magnetic resonance imaging (MRI) found a pituitary hypoplasia. Her two sisters had the same clinical presentation. Molecular analysis of PROP1 concluded to a homozygous mutation in three sisters.
Observation 2
We report the case of two sisters, born at term to healthy consanguineous parents. The index case was referred at the age of 14 years for delayed growth. Physical examination showed a short stature with a height of 131 cm (between −3 and −4 s.d.), a microcephaly, a saddle nose, a high-arched palate and female external genital organs with Tanner stage 1. Her bone age was eleven years. Hormonal investigations revealed a partial growth hormone deficiency, a corticotropin and gonadotropin deficiency. The pituitary MRI was normal. Her 8-year-old sister had an intellectual disability, and a delayed growth. She was 131 cm (< −4 s.d.) and had a digital agenesis. Hormonal investigations only showed a corticotropin deficiency. The pituitary MRI was normal. Molecular analysis is still ongoing.
Conclusion
These two cases highlight the disparities of the phenotype presentation, sharing only the consanguinity and short stature in the siblings, motivating the investigations and leading to the diagnosis of congenital hypopituitarism. Molecular analysis is recommended for the genotypic diagnosis and guides the familial investigations and genetic counseling.

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AEP640

Looking for cyclic cushing's syndrome

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Introduction
Cyclic Cushing´s syndrome (CCS) is a rare disorder with a wide clinical variability, characterized by repeated episodes of cortisol excess and periods of normal or even low cortisol secretion. Different periodical diagnostic tests are required to confirm hypercortisolism and thereafter imaging techniques and laboratory studies can be performed to localize the cause.
Case report
A 17-year-old female patient with a personal history of advanced puberty and non-treated obesity is admitted to Internal Medicine reporting myalgias, headache and a rapid weight gain of 15 kgs. Physical examination reveals facial plethora, violaceous striae, hirsutism and menstrual disorders. In conjunction with Endocrinology, initial laboratory testing is guided towards diagnosis of Cushing syndrome, but all results result normal. However, due to a great clinical suspicion, the study is prolonged and during the follow-up, alternating normal and abnormal tests are obtained. Petrosal sinus sampling is indicated concurring with abnormal 1 mg- dexamethasone suppression and pituitary magnetic resonance showed a 4 mm adenoma.

	08/02/19	01/03/19	20/03/19	08/04/19
24 h free cortisol µg/24 hours	43.86	36.46	**279.55**	44.53
Nugent µg/dl	0.84	**2.43**	**11.67**	
Cortisol 00:00 h µg/dl	0.88	**7.04**	**8.17**	5.95
Cortisol 8:00 h µg/dl	2.94		9.80	
Cortisol 20:00 h µg/dl	1.31		3.93	
ACTH pg/ml	23.1	37	28.8	21.5

	Petrosal sinus sampling		
	Peripheral	**RPS**	**LPS**
ACTH pg/ml	34.6	478.8	92.13
ACTH 5 minafter CRH pg/ml	73.9	80.3	53.4

A successful hemi-hypophysectomy is performed with great clinical improvement and an ACTH-producing pituitary adenoma is reported in the pathology sample.
Discussion
Cycles of hypercortisolism in CSS can occur regularly or irregularly with intercyclic phases ranging from days to years showing normal cortisol or even hypocortisolemia. The fluctuating clinical picture and discrepant biochemical findings make cyclic CCS sometimes extremely hard to diagnose.
Ethical aspects
The case has the informed consent of the patient.

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Medical treatment leading to remission of ectopic cushing's syndrome

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A 35 year-old lady presented to her local hospital with a 3 year history of fatigue, weight gain, recurrent tonsillitis and oligomenorrhoea. Examination revealed facial plethora, round facies and thin skin on the dorsum of the hand. She appeared tanned, with evidence of spontaneous bruising and difficulty standing up from a chair unaided. No striae were present. Blood pressure was 152/91 mmHg. Investigations revealed a 0900 h cortisol of 632 nmol/l (ACTH 59 ng/l) and an elevated UFC of 727 mmol/day. An ONDST failed to suppress at 520 nmol/l (0900 h ACTH 72 ng/l). A cortisol day curve showed loss of normal circadian rhythm, with cortisols ranging from 617–776 nmol/l. IGF-1 was elevated on numerous occasions, peaking at 380 microgram/l (81.2–278.1), with detectable GH of 4.43 mg/l, but without clinic features of acromegaly. MR pituitary was unremarkable. An IPSS did not show a peripheral-to-central gradient, suggesting ectopic ACTH production. The patient failed to respond both clinically and biochemically to high doses of metyrapone and was referred to our centre for further investigations. A cortisol day curve performed on a test dose of octreotide, showed an excellent biochemical response, with cortisol levels of less than 50 nmol/l. A block-and-replace regime, with octreotide and hydrocortisone, was hence commenced. No causative ectopic ACTH source was found on full scanning, including Ga-Dotatate PET-CT. However, a 12 mm enhancing lesion was seen within the left kidney, raising concerns for a possible renal cell carcinoma. The patient proceeded to left adrenalectomy and left partial nephrectomy. Histology confirmed a renal oncocytoma, with no post-operative change in cortisol levels. Long-term management options were discussed, including removal of the remaining adrenal gland. However, given that the patient was clinically well, a block-and-replace regime was opted for. Over the next few months, the pre-octreotide 0900 h cortisol rose from less than 50 nmol/l (ACTH 10 ng/ml) to133 nmol/l (ACTH 28 ng/ml). Detectable cortisol and ACTH levels could signify recovery of the HPA axis or tumour escape. A pre-octreotide ONDST showed complete cortisol suppression to 10 nmol/l, suggesting recovery of the HPA axis. The dose of hydrocortisone was tailed down until it was altogether stopped and the patient remains in clinical remission on monthly injections of octreotide. We are unaware of other cases in the literature of ectopic Cushing's managed with octreotide, where there has been full recovery of the HPA axis. We herein discuss the implications of this treatment in the medium to long-term.

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AEP642

An uncommon cause of atrial fibrillation

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Thyrotropin-secreting pituitary adenomas (TSHomas) are rare functioning pituitary adenomas, accounting for less than 1%. They commonly present as macroadenomas with symptoms of hyperthyroidism. Though surgery is the first line therapy, cure is achieved in only 30–40%, with high rate of post-surgical hypopituitarism. We propose somatostatin analogs having a new role in the management. We report a case of 73 years-old man with a 6-month history of palpitations and progressive dysnea due to an atrial fibrillation. Personal history of hypertension and colon cancer in remission. No family history of thyroid disease. He denied weight lost, visual symptoms, headache, iodine contrast or amiodarone intake. In hospital his heart rate was 130 beats/minute, blood pressure 140/60 mmHg. He had signs of heart failure and goiter. No visual defects were found nor dysthyroid eye disease. Initial thyroid biochemistry revealed a free thyroxine (FT4) concentration 3.95 ng/dl (0.93–1.70 ng/dl), TSH 5.49 µIU/ml (0.27–4.2 µIU/ml) and free triiodothyronine (FT3) 6.3 pg/ml (1.8–4.3 pg/ml), thyroid receptor antibody (TRAb): <0.6 IU/l (negative; <1 IU/l). Alpha subunit 8.1 IU/l (reference range <0.7 IU/l), alpha subunit/TSH molar ratio: 20, sex hormone binding globulin (SHBG) 186 nmol/l (10–57 nmol/), prolactin 17 ng/ml (4–15.2 ng/ml); other pituitary hormones were within the normal reference range. Thyroid ultrasound revealed a goiter with millimetric cystic nodules. The TRH test after 200 mg of TRH iv showed a blunted response: TSH 4.30 at 0 minutes; 4.20 at 20 minutes; 4.10 at 40 minutes; 4.10 at 60 minutes. The pituitary MRI revealed a sellar lesion of 13 mm, with suprasellar extension but without cavernous sinus invasion. Thus, a thyrotropin-secreting pituitary adenoma was suspected but the patient refused surgery and radiotherapy. We started octeotride LAR 20 mg i.m. treatment every 28 days. After six months FT4 decreased to 1.49 ng/dl, TSH to 0.55 µIU/ml and FT3 to 2.42 pg/ml all of them within the normal range. The MRI showed a 7 mm sellar lesion. After 2 years, the patient is in good clinical condition, with no hospital admissions, thyroid hormones are within the normal range and the sellar lesion is stable.

Conclusion

This case supports the increasing evidence of somatostatin analogs as primary therapy in the management of some thyrotropin-secreting pituitary adenomas achieving excellent biochemical and radiologic response.

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AEP643

Osmotic demyelination syndrome in a patient with noonan syndrome and anterior hypopituitarism

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Introduction

Management of severe hyponatremia is challenging because of the need to balance the risk of overcorrection leading to osmotic demyelination syndrome (ODS) as well as under-correction causing complications, particularly in a patient with hypocortisolism and hypothyroidism. Case reports of patients with Noonan syndrome with hypopituitarism are rarely reported in literature. We report a case of a patient with Noonan syndrome and untreated anterior hypopituitarism who presented with symptomatic hyponatremia and developed transient episode of ODS.

Case Presentation

A 50-year-old male presented with a two-day history of insomnia, severe nausea and dizziness. He was found to have hyponatremia (109 mmol/l). A thorough history taking revealed that he was found to have chronic anterior hypopituitarism with hypocortisolism, hypothyroidism and hypogonadism with 2 previous hospital admissions of severe hyponatremia in the last 15 years. However, each time, he would stop his hormonal treatment after a year and currently has stopped allmedications for 8 years. On examination, he had typical features of Noonan syndrome. He also had clinical features of hypogonadism which were bilateral gynecomastia, very small testes, and absent facial, pubic, and axillary hair. Initially, the sodium level risen from 109 mmol/l to 113 mmol/l over 22 hours. Despite careful administration of small volume of fluid (only 150 mls normal saline), hydrocortisone and levothyroxine replacement, his sodium level risen to 123 mmol/l over the next 15 hours. He developed a transient acute episode of hypertonia and aphasia due to ODS. Intravenous dextrose 5% fluid and desmopressin were used to lower his sodium level and his symptoms resolved. He made full recovery on discharge. Compared to his magnetic resonance imaging (MRI) pituitary fossa scanperformed 8 years ago which showed a non-enhancing 2 mm lesion in the left pituitary gland likely a non-functioning micro-adenoma, his repeat MRI pituitary scan was normal currently.

Conclusion

Patients with hyponatremia from chronic anterior hypocortisolism and hypothyroidism are a high risk of ODS. Careshould be taken to avoid a rise of >4–6 mmol/l per 24 hours. Early recognition, rescue desmopressin and dextrose 5% fluid to reduce serum sodium concentration were helpful to treat acute ODS.

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AEP644

A case of developmental delay by 18q23 deletion syndrome

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Introduction

Monosomy 18q represents a partial deletion of the long arm of chromosome 18, with an estimated prevalence of 1:100 000. This syndrome is characterized by a highly variable phenotype. The symptoms and their severity depend on which part of the chromosome is missing. Most common manifestations are hypotonia, developmental delay, short stature, growth hormone deficiency, hearing loss and external ear anomalies, intellectual disability, palatal defects, dysmorphic facial features, skeletal anomalies, and mood disorders.

Case presentation

The patient, a 14 year old male, was first evaluated at the Pediatrics Department due to mild cognitive delay, postnatal proportional short stature, and absence of pubarche. He was born at 39 weeks old, with abnormal weight (46 cm, < 5th centile, –2.1 SDS). He had dysmorphic features, hypotonia, his heigh was 141 cm (< 5th percentile, – 2.7 SDS) and his body mass index (BMI) was 14.8 (–2.58 SDS) and Tanner stage 1. The lab tests showed hemoglobin 15.4 g/dl (13.9 – 16.3), IGFBP-3 3.22 (3.3 – 10), IGF1 91 (173 – 414), LH 1.2 mIU/ml (1.2 – 8.6), FSH 1.6 mIU/ml (1.3 – 19.3), total testosterone 0.4 ng/ml (1.6 – 7.5), free testosterone 0.36 pg/ml (0.3 – 1.7), TSH 3.23 mUI/ml (0.38 – 5.33), with negative celiac disease screening, normal phospho-calcium metabolism, hemoglobin, renal, glucose and lipid profile. The bone maturation was 3 years delayed concerning his chronological age. The clonidine test suggested GH insufficiency. Cerebral MRI was unremarkable. Genetic study: 18q23 deletion in an array and confirmed in FISH. Karyotype 46, XY, del (18) (q23). He started supplementation with testosterone 50 mg every 4 weeks. He transitioned to adult Endocrinology department at 18 years old and maintained testosterone supplementation. He had a normal testes. Testicular ultrasound: normal testicular. Echocardiogram and renal ultrasound, performed to screen for comorbidities associated with this syndrome, found no changes. In the last evaluation: Weight: 41.5 kg (< 5th percentile, – 4.1 SDS), height: 161.5 cm (< 5th percentile, –2.1 SDS). Tanner 5. Hormonal evaluation showed normal gonadotropins and testosterone, prompting testosterone deficiency reassessment.

Discussion

This case shows an uncommon cause of GH insufficiency. In patients with 18q23 deletion syndrome, GH deficiency is common, and there are case reports of concomitant hypothyroidism. In this case, the patient had, in addition to GH deficiency, an initial hypogonadotropic hypogonadism which has not been previously described.

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AEP645

Sodium copeptin ratio differentiates patients with and without acute diabetes insipidus post neurosurgery

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Background
The diagnosis of central diabetes insipidus (DI) relies on indirect measurement of serum/urine sodium and osmolality. Since the diagnosis can only be made when an inappropriately dilute urine is paired with a significantly concentrated serum, the process is tedious for the clinician and uncomfortable for the patient. Copeptin is the C-terminal portion of the anti-diuretic hormone (ADH) prohormone which correlates with the less stable ADH, therefore providing a direct measurement of posterior pituitary response to hyperosmolar stress[1,2].
Aim
This study aims to assess the diagnostic accuracy of copeptin in patients with central DI compared with subjects who underwent pituitary surgery without DI.
Methods
Serum samples from subjects with central DI, control subjects post pituitary surgery with no DI (NDI) and control subjects with SIADH were collected and analysed on the BRAHMS KRYPTOR copeptin assay. Groups were compared using unpaired T-test and Levene's test for equal variance.
Results
56 samples from 22 subjects (13 females, nine males, mean age 53.9±15.5 y.o.) were analysed. Two subjects had resolved DI (RDI) after copeptin analysis and were successfully weaned off DDAVP and reclassified as NDI. Of the DI subjects, 1 had acute and 5 had chronic DI. Copeptin was lower in DI compared to NDI group ($P=0.013$), while serum sodium, osmolality, urine osmolality were similar. Copeptin did not differentiate between the SIADH and NDI groups. After exclusion of NDI samples with serum sodium ≤140 mmol/l, the area under the curve was 0.97 (95% CI 0.9 to 1.0), a copeptin cut-off of 2.9 pmol/l predicts DI with a sensitivity of 92% and a specificity of 90%.

Table Biochemical parameter between groups.

	DI	NDI	SIADH
No.	6	12	4
Age (years)	42±16 #	56±13	67±14
Serum Na (mmol/l)	142±9 #	139±2	122±4 *
Serum Osmol	289±15 #	290±5	253±0.7 *
Urine Osmol	371±203	635±219	445±216
Copeptin (pmol/l)	1.89±0.59 *	12.98±13	22.68±34.45

* $P<0.05$ vs NDI, # $P<0.05$ vs SIADH.

Conclusion
Copeptin concentration of <3.0 pmol/l concurrently with serum sodium concentration of >140 mmol/l predicted central DI when using post pituitary surgery subjects without DI as controls.
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AEP646

Differences in acquired and idiopathic adult-onset growth hormone deficiency

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Introduction
Growth hormone deficiency (GHD) is a medical condition affecting adults and children who lack sufficient growth hormone. The objective of this study was to compare diagnoses in acquired and idiopathic adult-onset GHD patients.
Methodology
Results are from Ipsos' EU5 GHD Therapy Monitor Study 2018, which is an online study conducted among physicians treating both paediatric and adult GHD patients. 156 sampled physicians provided data on the last 5 consecutive GHD patients (reporting on 779 patients) seen between November 2018 and January 2019. Data included demographics, comorbidities, diagnostic tests, disease history, and treatment patterns. Descriptive analysis was conducted using appropriate statistical tests.
Results
Two thirds (66%) of adult-onset GHD patients ($n=220$) treated by endocrinologists in the study have acquired GHD, whilst the remaining have idiopathic GHD. Specific tests used to confirm diagnosis in the two types of patient groups varies slightly. Adult-onset patients with acquired GHD are significantly more likely to have their diagnosis confirmed using an IGF-1 blood test than those with idiopathic GHD (89% vs 70%, $P<0.01$). Idiopathic patients are significantly more likely than acquired patients to have had a hand X-ray (27% vs 6%, $P<0.01$) and/or karyotyping (26% vs 3%, $P<0.01$) tests to confirm diagnoses of GHD. Unsurprisingly, when looking at types of tests idiopathic GHD patients are significantly more likely to have genetic testing than those with acquired GHD to confirm diagnosis, likely due to the nature of the condition. While fatigue is the most common first symptom observed among the adult-onset GHD patients, data suggest it is more likely to impact acquired GHD patients than idiopathic patients (79% vs 47%, $P<0.01$). Significantly more adult-onset patients with idiopathic GHD present with truncal obesity (45% vs 27%, $P<0.01$) and dry skin (38% vs 21%, $P<0.01$) than patients with acquire GHD.
Conclusion
There is a lack of standard diagnostic criteria for both acquired and idiopathic GHD leading to potential delays in diagnoses for the patient population. This study highlights the differences in first symptoms and diagnostic tests between idiopathic and acquired adult-onset GHD patients. Further research is needed to understand which diagnostic tests are being used in each type of GHD in order to identify a more standardised approach to diagnosis.
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AEP647

Evaluation of the of alpha2-adrenergic receptors stimulation effect on copeptin secretion, based on the result of the test with clonidine used in the diagnosis of children with short stature

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Introduction
Copeptin can be used as a tool to directly assess serum antidiuretic hormone (ADH) level. A certain pool of ADH are synthesized in hypothalamus, together with corticoliberin (CRH). Then they are released into the pituitary portal circulation, where through the V1bR receptor ADH stimulates adrenocorticotropic cells and ACTH secretion, followed by cortisol and catecholamines production. The stimulus for ADH secretion is, among others, stress. In turn, presynaptic stimulation of the α 2 receptor inhibits the secretion of noradrenaline. On the other hand, stimulation of the alpha2-receptor is widely used in the diagnosis of growth hormone deficiency (GHD) in children. Clonidine, by stimulation of the presynaptic alpha2-adrenergic receptor, in addition to inhibiting the release of noradrenaline, stimulates the secretion of somatoliberin (GHRH) from the hypothalamus, which in turn stimulates the synthesis of GH. Because other possible ADH effects on the pituitary have not been recognized so far, we decided to evaluate the effect of stimulating alpha2-adrenergic receptors after clonidine administration

on copeptin, as well as to assess the differences in response to the above mentioned stimulation in groups of children with normal and decreased GH secretion (ISS and GHD groups).
Material and methods
The serum concentrations of copeptin, GH, cortisol and ACTH at individual time points (0', 30', 60', 90' and 120') during the 2-h stimulation test for GH secretion after oral clonidine administration at a dose of 0.15 mg/m^2 were assessed. The test was carried out for diagnostic purposes in 49 children (mean age± S.D.: 9.55 ± 3.48 yrs) with short stature (height < − 2.0 S.D.). In 29 children ISS and in 20 GHD were diagnosed.
Results
We did not find any differences between copeptin concentration in groups of GHD and ISS children. In both groups (GHD and ISS children), a significant reduction in copeptin secretion after clonidine administration was observed: mean pg/ml ± S.E.M.: 0'–460.5 ± 103.7; 30'–369.0 ± 74.4; 60'–353.1 ± 75.7; 90'–339.0 ± 63.1; 120'–376.1 ± 73.0. ACTH and cortisol levels also decreased with consecutive withdrawals during the stimulation test for GH secretion.
Conclusions
Short-term adrenergic stimulation of alpha2-receptors (after oral clonidine administration) seems to influence (reduce) copeptin secretion in children with short stature in both the ISS and GHD groups.

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AEP648

Typical carcinoid of the nose: The role of somatostatin agonist following surgery

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Carcinoid tumors (CT) seldom develop in the head and neck area. Several authors doubt the existence of authentic neuroendocrine tumors in the nose. Most of the CT arise in the larynx.
Clinical case
A 54 years old woman, who had a right-sided nasal obstruction, rhinorrhea, and sometimes purulent discharge in 2016. In 2002 she had hyperthyroidism by Graves disease and treated for two years with remission after that. The examination of the nose revealed a dark red bleeding mass filling the area from the right nasal cavity to the nasopharynx. The biochemical and serum hormonal values were in a normal range. Urine 5 -HIIAA was 2,5 mg/24 h. MRI T1 and T2-weighted images revealed a mass fo 4.1 × 4.2 cm, slightly higher signal in T2 and isointense in T1, that extended into the right nasal cavity and ethmoidal sinus. A biopsy was performed, which revealed CT. Octreoscan with SPECT showed an intense nasal uptake. Right internal maxillary artery embolization was performed. In the next two days, the tumor was resected through a right lateral rhinotomy. Histopathological examination revealed neuroendocrine tumor low grade, ki67 < 2%. Positive immunohistochemical staining to CD56, synaptophysin and chromogranin A, and a negative one to CK. The resection was almost total, with no octreoscan uptake. The post MRI revealed a minimal residual lesion. Lanreotide treatment was introduced after surgery; the dose was 120 mg every four weeks the first year and every 8 weeks after that. No secondary effects or biochemical alterations were observed.
Discussion
A limited number of cases have been reported for CT arising in the nose. As in our case, the majority of typical carcinoids are non-functional. The patients mainly complain of local symptoms such as nasal congestion. Surgery is considered to be the first-line treatment for localized disease. In the case of a close margin of the lesion or a residual tumor, the recommendation was radiotherapy or chemotherapy for more advanced disease. We confirm that the tumor expresses somatostatin receptors. We treated the residual tumor with lanreotide with no progression of the disease after three years of follow-up. The somatostatin analogs may be a useful adjuvant therapy for stable residual disease. We have done a review of the published cases

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AEP649

Multi-hormonal secretion in a young male with a large cystic pancreatic neuroendocrine neoplasm

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Introduction
The molecular pathogenesis of pancreatic neuroendocrineneoplasms (PNEN) is increasingly yet incompletely understood. PNEN typically occur sporadically or may occur within the context of hereditary tumor predisposition syndromes. PNEN can also be associated with endocrinopathy of hormonal hypersecretion. We present a young male with a multi-hormonal neuroendocrine neoplasm of pancreas.
Case presentation
A 24-year-old male, non-smoker, with a history of epileptic seizures, hypophyseal Rathke cyst and tonsillectomy presented with hypoglycemias. Family history was unremarkable. Prolonged fasting test was indicative for insulinoma. Abdomen CT was performed and showed a 4 cm cystic lesion of the pancreatic tail. EUS with FNAB was performed and the cytological result was compatible with PNEN. The patient underwent distal pancreatectomy. Histology revealed a well differentiated PNEN, Grade 2 (Ki67 6%), CgA (+), Syn (+), SSTR2a (+), insulin (+), Glucagon (–) with insulin production. Moreover, another small lesion of well differentiated PNEN (1.3 mm) Grade 1 (Ki67 1%), CgA (+), Syn (+), SSTR2a (+), Glucagon (+), insulin (–) with glucagon production was histologically found. Due to the young age of the patient and multi-hormonal appearance of the neoplasm, a gene analysis for MEN1 and VHL was performed and was negative.
Conclusion
This is a rare case of functional PNEN with two different pancreatic lesions producing competitive hormones. The clinical symptoms are compatible with the larger producing neoplasm.

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AEP650

Differentiation of Insulinoma from accessory spleen by 99mTc-labelled heat-denaturated red blood cell scintigraphy

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Introduction
Neuroendocrine tumors (NETs) are rare tumors harboring overexpression of somatostatin receptors (SSTRs) on their cell membrane. Gallium 68-tetraazacyclododecane tetraacetic acid-octreotate (68Ga-DOTATATE) positron emission tomography/computed tomography (PET/CT) is an important imaging modality in diagnosis and staging of NETs. Because some organs such as spleen, adrenal glands and liver physiologically express SSTR, it might be challenging to distinguish some pancreatic NETs located in the pancreatic tail from accessory spleen next to the splenic hilum. In this manuscript, we report a case with hypoglycemia attack and 2 different masses displayed by 68Ga-DOTATATE PET/CT.
Case Report
A 63-year-old woman presented to the emergency with profuse sweating and light-headedness. Her blood glucose level was 45 mg/dl (2.5 mmol/l) and dextrose 5% infusion was started immediately. In the first hour after cessation of infusion, symptomatic hypoglycemia was developed with high insulin and C-peptide levels, 41 µIU/ml (1.9 – 23) and 12.7 ng/ml (0.9 – 7.1), respectively. The levels of antibodies to endogenous insulin were normal. Insulinoma was suspected and endoscopic ultrasonography (EUS) was planned, but it could not be performed. As a result, 68Ga-DOTATATE PET/CT was applied. It revealed two masses with increased tracer uptake located adjacent to the splenic hilum and inferior pole of the spleen which were reported as accessory spleens. 99mTc-labelled heat-denaturated red blood cell (99mTc-HDRBC) scintigraphy was applied to distinguish a NET in the

pancreatic tail from accessory spleen at the splenic hilum. Enhanced tracer uptake remained in the inferior pole of spleen, but not in the splenic hilum. The lesions were suggestive of insulinoma in the pancreatic tail and an accessory spleen adjacent to the inferior pole of spleen. Hemipancreatectomy and splenectomy were performed. The histopathological findings revealed a grade 1 pancreatic neuroendocrine tumor.
Discussion
99 mTc-HDRBC scintigraphy is a beneficial imaging method to display the functional splenic tissue. Therefore, it may be a reasonable imaging option to distinguish splenic tissue from NETs or their metastases. The basic mechanism of this imaging technique is based on denaturated red blood cell uptake by functioning spleen for the removal of abnormal erythrocytes. As described in our case report, 99 mTc-HDRBC scintigraphy is a useful nuclear medicine method to differentiate a NET in the pancreatic tail from accessory spleen at the splenic hilum. In conclusion, 99 mTc-HDRBC scintigraphy is a practicable specific diagnostic technique which may avoid unnecessary surgeries in the presence of enhanced tracer uptake or vice versa.

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AEP651

Predictors of Cushing's disease remission after transsphenoidal endoscopic surgery

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Purpose
The postoperative levels of cortisol and ACTH are the most commonly used markers for the prediction of Cushing's disease (CD) remission after transsphenoidal surgery (TSS). However, there is still no consensus on the collection time and threshold values of basal cortisol and ACTH levels after surgery to predict remission of CD.
Aim
To study the significance of early postoperative serum cortisol and plasma ACTH testing in the prognosis of CD remission after TSS.
Materials and methods
101 patients with Cushing's disease (12 men, 89 women, mean age 41 years (15–72) confirmed after TSS were included. In all patients basal morning serum cortisol and plasma ACTH at 2 days and at 14 days postoperatively were measured. The results of TSS were evaluated one year after surgery Remission criteria were: secondary adrenal insufficiency or combination of normal midnight ACTH and serum cortisol levels, normal 24-hour urine free cortisol (UFC) excretion and serum cortisol suppression less than 50 nmol/l in 1-mg dexamethasone test. The optimal threshold value of hormone levels for prediction of CD remission after TSS was calculated by ROC-analysis.
Results
One year after surgery CD remission was confirmed in 63 patients, whereas in 38 patients hypercortisolism persisted. The optimal value of basal serum cortisol at 2 days after TSS for prediction of CD remission was ≤388 nmol/l, with sensitivity 94,9% and specificity 75,9% ($P<0.001$), and for 14 days it was ≤417,7 nmol/l, with sensitivity 96,4% and specificity 87% ($P<0.001$). The optimal value of plasma ACTH at 2 days was ≤20 pg/ml with sensitivity and specificity 83.3% and 95.8% respectively ($P<0.001$), and at 14 days it was ≤41.71 pg/ml, with sensitivity and specificity 94.4% and 88.9%, respectively ($P<0.001$).
Conclusion
Serum cortisol and plasma ACTH levels had a comparable high predictive accuracy when measured at 2 days and 14 days after surgery in the prediction of CD remission after TSS. High threshold values of serum cortisol and plasma ACTH in our study could be explained that not only specificity, but sensitivity were calculated for both markers.

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AEP652

Acrodat – a useful tool to manage acromegaly patients

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Introduction
Acromegaly is a rare condition associated with metabolic abnormalities, risk of cardiovascular complications and increased mortality. Even when biochemical control is achieved, following surgery or medical treatment, patients still complain about disease-related symptoms.
Material and methods
Retrospective study of acromegaly patients, followed in an Endocrine outpatient clinic. Clinical and biochemical data was recorded. ACRODAT was used to easily understand if patients were controlled, if they were symptomatic or if they had comorbidities [diabetes; cardiovascular disease (CD); sleep apnea] before and after treatment. Symptoms were evaluated by *Signs and Symptoms Score* (SSS). Surgical cure and biochemical control were considered to be an insulin growth factor-1 (IGF-1) value less than once the upper limit of normal (ULN) for sex and age. Descriptive and inferential statistics were used, with significance level $\alpha=0.05$.
Results
Twenty-nine patients were evaluated – mean age=48 years-old (11–80); mean follow-up time=63 months (11 – 106). Ten patients achieved disease control following surgery. First evaluation, before surgery: mean IGF-1=2.63 above ULN; 7 patients were symptomatic [median SSS score=9 (6–18)]; 5 had comorbidities. Last evaluation after surgery: mean IGF-1=0.77 above ULN; 2 patients were still symptomatic [median SSS score=2 (1 – 3) – $P=0.018$]; 7 had comorbidities – among these, there was one patient who resolved sleep apnea. Ten patients were controlled with medical therapy, after non-curative surgery. First evaluation, before surgery: mean IGF-1=2.88 above ULN; 7 patients were symptomatic [median SSS score=6 (4 – 25)]; 4 patients had comorbidities. Last evaluation after surgery: mean IGF-1=0.78 above ULN; 4 complained about symptoms [median SSS score=6 (2 – 10) – $P=0.046$]; 5 patients had comorbidities – among these, there was a patient with new-onset diabetes, another developed CD and another with complains about sleep apnea. Four patients are waiting for surgery; three are still uncontrolled despitesurgery and medical treatment; two patients have died (one because convulsive crisis and another because of pneumoniae and end-stage renal failure). Because this is a retrospective study, it wasn't possible to collect data about quality of life.
Conclusions
ACRODAT is a useful tool in the follow-up of acromegaly patients. It allows us to evaluate symptoms in a measurable manner, and to understand better how the disease impairs patients' lives. It may help making treatment decisions. Another advantage relates to comorbidities: allowing to report the ones that improve and the new-onset diabetes, CD and sleep apnea. With this registry it's possible to manage better each particular patient.

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AEP653

Characterization of pituitary adenomas by immunohistochemistry of pituitary-specific transcription factors and their correlation with hormonal subtypes

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Introduction
The immunohistochemical characterization of Pit-1, Tpit and SF-1 transcription factors allows the identification of the three adenohypophyseal cell lines and has been incorporated into the latest WHO classification of pituitary adenomas (PA). The aim of the present study was to quantify the protein expression of pituitary-specific transcription factors (TF) by immunohistochemistry (IHC) and to correlate these results with the identification based on hormonal protein expression. Moreover, to validate these results by qRT-PCR in a subset of samples.
Material and methods
We selected 144 PA with complete information. These adenomas had been previously classified according to the IHC of the pituitary hormones: 18

densely granulated somatotroph adenomas (DGSA), 17 sparsely granulated somatotroph adenomas (SGSA), 9 lactotroph adenomas, 49 gonadotroph adenomas, 18 corticotroph adenomas and 29 null cell adenomas. We quantified the immunohistochemical expression of Pit-1 (PA5–59662), Tpit (ab243028) and SF-1 (ab217317) (cutoff 5%) on Tissue Microarrays. We quantified the relative gene expression of TPIT, PIT-1, SF-1, GATA2 and ESR1 by qRT-PCR.
Results
The mean age of the patients was 54 years, 65 were women and 79 men. Three cases were eliminated due to their double tumor nature. 49 PA were Pit-1 IHC positive of which 18 expressed GH, 14 GH and PRL, 8 PRL, 2 TSH, 1 LH and TSH and 6 were null. 19 were Tpit IHC positive of which 10 were Cushing (expressed ACTH) and 9 were silent (8 expressed ACTH and 1 was only Tpit). 67 expressed SF-1 by IHC of which 49 expressed FSH/lH and 18 only SF-1, without hormonal expression. 6 tumors were confirmed as null. Moreover, gene expression of TF agreed with the IHC identification.
Conclusion
The IHC study of the expression of pituitary-specific TF proteins allows a better identification of PitNETs, significantly reducing the percentage of null cell tumors.

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AEP654

Our experience with lu-dotatate in patients with neuroendocrine tumors in a tertiary hospital

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Introduction
Lutetium-177-DOTATATE (Lu177) is approved in patients with well-differentiated (G1 and G2) neuroendocrine tumors (NETs) positive to somatostatin receptors, progressive and unresectable or metastatic. Lu177 has been shown to increase progression-free survival and the quality of life of these patients.
Material and methods
Retrospective descriptive study of a series of 15 cases with NETs treated with Lu177. Demographic data, tumor characteristics, previous and concomitant treatments, response to Lu177 treatment and possible adverse reactions have been collected.
Results
We describe 15 patients, 9 men and 6 women with 62±11 years old of average age. The location of the primary tumor was ileum in 7 patients, pancreas in another 7 and lung in 1. Regarding the degree of differentiation, 5 were G1 (33%), 8 G2 (53%) and 2 G3 (13%). All of them presented liver metastases, 7 lymphatic, 2 bone, 4 peritoneal implants and 1 ovarian metastases. 11 of them were functional, the remaining 4 were not. As a concomitant treatment, everyone was receiving somatostatin analogues (13 lanreotide and 2 octreotide). As previous treatments, 6 had received everolimus, 4 chemotherapy with cisplatin+etoposide and 5 intrahepatic treatment (embolization with yttrium spheres). In all of them uptake was visible in scintigraphy with analogues prior to treatment with lutetium. 11 patients completed the 4 doses of 200 mC1, 1 received 3 cycles, another 2 cycles and 2 patients 1 cycle. The follow-up time was 6 to 42 months. The radiological response of the lesions (according to RECIST 1.1 criteria) was partial response in 3 patients (27%), stabilization in 2 (18%) and tumor progression in 6 (54%) of them (2 exitus for this reason). In the 5 patients with partial response or tumor stabilization there was also a metabolic response mesured by Octreoscan and a biochemical response with decreased levels of Chromogranin A. 4 are waiting to complete the cycles. Adverse reactions have all been self-limited, the most frequent were gastrointestinal (nausea 26% and vomiting 20%), mild thrombocytopenia(26%), mild anemia (6.6%) and mild neutropenia (6.6%). No anaphylaxis or nephrotoxicity reactions have been observed.
Conclusions
In our experience, treatment with Lu177 in patients with metastasic NETs has been able to control the disease in 45% of the patients that completed the 4 cycles with mild gastrointestinal and hematological adverse effects. Lu177 treatment is an excellent therapeutic option, as long as it is decided within the consensus of a multidisciplinary team.

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AEP656

Characteristics of severe forms of Cushing's disease compared to milder cases

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Introduction
Cushing's disease (CD) is associated with significant morbidity and mortality due to cerebro-cardiovascular, thrombotic or infectious complications. However, there is significant variation in the clinical presentation and consequences of hypercortisolism, resulting in a wide clinical spectrum, ranging from mild to severe or even life-threatening disease requiring immediate treatment.
Aim
The description of patients with severe CD in comparison with milder forms, with regards to their clinical characteristics and outcome.
Patients and methods
171 patients with CD (144 females), mean age 45±14 years who were admitted in our Department. We defined biochemically severe CD (BCD, $n=19$) by serum cortisol more than 36 μg/dl at any time or a 24-h urinary free cortisol > 4 × ULN and/or severe hypokalaemia (<3.0 mmol/l), and as clinically severe CD (CCD, $n=15$) the presence of one or more of the following: sepsis, opportunistic infection, uncontrolled hypertension, heart failure, acute psychosis, progressive debilitating myopathy, thromboembolism or uncontrolled hyperglycaemia. Patients fulfilling both criteria were defined as severe CD (SCD, $n=21$). The remaining patients were defined as non-severe CD (NSCD, $n=116$).
Results
There were no differences in age and mean adenoma size among groups; the prevalence of macroadenomas was 27% in NSCD patients, 16% in BCD, 27% in CCD and 14% in SCD. Baseline ACTH levels were higher in BCD and SCD groups compared to CCD and NSCD groups and the ACTH-to-cortisol ratio was similar among groups. Early, 90-days-mortality from sepsis/opportunistic infections was observed in 3 (20%) patients with CCD and 2 (9.5%) patients with SCD, despite medical aggressive management with ketoconazole and metyrapone. When only patients with long-term follow-up (>2 years, mean follow- up time 4.7±2.8 years) were considered ($n=120$), bilateral adrenalectomy to control hypercortisolism was performed in 27% of BCD, 38% of CCD and 31% of SCD, compared to only 8.6% of NSCD patients. Long-term mortality (mean time to death after diagnosis 10.9±5.8 years) was higher in SCD (19%) and BCD (13%) vs 2.5% in NSCD.
Conclusions
Cushing's disease remains a detrimental disease with significant early and late mortality, especially in patients presenting with severe biochemical and/or clinical hypercortisolism.

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AEP657

The impact of variations in laboratory measurements of IGF-1 and random growth hormone on the classification of acromegaly disease activity status: Lessons from the UK Acromegaly Register Reference Laboratory

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Background
The UK Acromegaly Register contains data for 2700 patients. IGF-1 and random growth hormone (GH) measurements are used for disease monitoring. The registry reference laboratory (RRL) uses the Immunodiagnostic systems (IDS)-iSYS immunoassay platform for GH and IGF-1. The RRL uses age- and sex-specific reference ranges for IGF-1. We compared IGF-1 and GH results fromlocal laboratories to those of the RRL (pre-defined as

the Gold standard) to determine the extent of differences and the implications for classification of disease activity status.
Methods
Blood samples were separated for local (IGF-1 *5 centres*, GH *4 centres*; Table 1) and paired RRL analysis. Controlled disease was defined for IGF-1 as below the upper-limit of the laboratory reference range and for GH as <1 mg/l. We calculated the RRL vs local assay correlation co-efficient and percentage bias and also compared respective disease activity status classifications between individual centres and the RRL.
Results
The total number of IGF-1 and GH measured were 277 and 121 respectively. Key results are summarised in Table 1.

Table 1

Centre	Analyser	No. of paired samples	Correlation with RRL	% bias	Number of discordantly *elevated* readings§ (%)	Number of discordantly *normal* readings§ (%)
			IGF-1			
1	Mediagnos-RIA-CTI	39	0.97***	+ 11.2	1(3)	9(23)
2	Siemens-Immulite-Xpi-2000†	45	0.91***	+6.5	3(7)	0
3	Siemens-Immulite-Xpi-2000†	128	0.96***	+ 10.8	12(9)	6(5)
4	IDS-iSYS†	19	0.80***	+ 7.3	0	0
5	IDS-iSYS†	46	0.88***	– 1.53	2(4)	3(7)
			GH			
1	Siemens-Immulite -Xpi-2000	43	0.97***	+ 12.1	4(9)	1(2)
2	Siemens-Immulite -Xpi-2000	40	0.83***	+ 8.31	1(3)	3(8)
3	Beckmen-Unicell	16	0.92***	– 15.2	0	0
4	Siemens-Immulite -Xpi-2000	22	0.99***	– 1.26	1(5)	0

***P*-value <0.001.
†Inter-laboratory differences in IGF-1 reference range despite same analytical platform.
§RRL definition of disease activity status was considered as the Gold standard; an elevated result in the local laboratory was classified as normal in the RRL (discordantly *elevated*) or local result was deemed normal but regarded as elevated at the RRL (discordantly *normal*).

Discussion
Our results show a relatively modest bias and strong correlation between local and RRL IGF-1 values. Consequently, differences in disease activity classification may predominantly represent inter-laboratory IGF-1 reference range variances. There were differences in the bias and accuracy of GH measurements (compared to RRL) of local laboratories even when utilising the same analytical platform. Further standardisation, traceability and commutability of assays and harmonisation of reference ranges might improve biochemical monitoring thereby potentially enhancing clinical decisions.

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AEP658

Prevalence of non-alcoholic fatty liver disease in patients with Cushing disease (CD)

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Introduction
The prevalence and comorbidities of NAFLD in CD are unknown. There is only one study wich set the prevalence of NAFLD by CT images in 20%[1].
Objectives
Describe the prevalence of NAFLD and fibrosis in CD and analize predictive biomarkers of NAFLD
Methods
Transversal descriptive study. 31 patients with CD; 11 active, 20 cured. Women 24 (77%), men 7 (23%). 54 years mean age. NAFLD was valorated by Hepatic Steatosis Index (HSI) and Controlled Attenuated Parameter (CAP dB/m). Fibrosis stage by FIB4 and transition elastography (kPa). Date of control of hypercortisolism was determinated by normalization of free urinary cortisol 24 hours.
Results
31 patients. 20 (65%) cured (11 with hydrocortisone treatment) and 11 (35%) with active disease, 3 (10%) non controlled. HTA 14 (45%), dyslipemia 16 (52%), type 2 Diabetes 7 (23%). Obesity (BMI > 30 kg/m^2) 15 (48%) and 10 (32%) overweight. 3 patients with previous mayor vascular event. Pathologic HSI (> 36) in 24 (77%). NAFLD clasiffication by CAP: S1 (248–268 dB/m): 3 (10%); S2 (268 –280 dB/m): 3 (10%); S3 (> 280 dB/m): 9 (29%); S0 en 16 (51%). All patients with HIS > 36 were classified as S2-3 with a correlation between HSI and CAP (coef 0,416). Besides, an association between NAFLD and active CD was observed (80% Vs 20%, *P* 0.07) NAFLD was also associated with obesity (83% vs 26%, *P* = 0,03), presence of DM, HTA and/or DLP (92% vs 53% *P* = 0,046) and longer time to get hormonal control (117 vs 29 months, *P* = 0,001). 3 (9.7%) patients with ET values >8.9 Kpa (F3-F4). All ET > 89 K Pa patients presented HSI > 36, but no one pathologic FIB4 value. ET > 8,9 kPa was associated with longer time to get hormonal control.
Conclusions
– A high prevalence of NAFLD has been observed in our series, with higer prevalence in non cured patients.
– HSI formula classified correctly NAFLD patients.
– FIB4 seems not to be a godo predictor of fibrosis.
Reference
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AEP659

Tumour progression in clinically non-functioning pituitary adenomas-does somatostatin analogue therapy decrease the risk?

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Introduction
The management of clinically non-functioning pituitary adenomas (NFPA) remains a debated issue. Surgery, which is indisputably indicated in invasive NFPA, is rarely curative. Moreover, it is not always feasible due to potential complications or contraindications. Expression of somatostatin receptors (SSTR) form the rationale for the use of somatostatin analogues (SSA) in NFPA.
Aim
To compare the risk of NFPA progression in patients treated with SSA vs those without pharmacotherapy.
Material and methods
57 patients with NFPA (subgroup A-40 after incomplete surgery + subgroup B-17 not operated) were enrolled into the study. SSTR scintigraphy and additionally immunohistochemistry (subgroup A) were performed. The presence of SSTR was confirmed in 25 patients (17 from subgroup A + 8 from subgroup B) in whom SSA therapy was started (every 4 weeks: octretide LAR 20 mg intramuscular or lanreotide autogel 120 mg deep subcutaneous injection). The duration of the therapy varied from 16 months to 18 years. Adenoma size was estimated in pituitary magnetic resonance imaging.
Results
Tumour progression rate was twice higher in patients who were not treated with SSA (71.9% vs 36%). In subgroup A tumour volume increased in 35.3% patients treated with SSA compared to 74% those without pharmacotherapy. Moreover, in subgroup B tumour progression was noticed in 37.5% SSA treated patients vs 66.7% not SSA treated patients.
Conclusions
SSA significantly decrease the probability of tumour progression in NFPA, however, further studies should be carried out.

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AEP660

Predictors for remission after transsphenoidal surgery in acromegaly: A dutch multicenter study

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Context
Transsphenoidal surgery (TSS) is the primary treatment of choice in acromegaly. It is important to identify patients in whom surgical cure is not attainable at an early stage, both to inform patients on expected treatment outcome and to select those who are more likely to need additional therapy.
Objective
To identify predictors for remission and relapse after TSS in acromegaly.
Design
Retrospective study in three large tertiary neurosurgical referral centers in the Netherlands.
Methods
We analyzed clinical data since 2000 from three cohorts (Rotterdam, Groningen and Nijmegen, total $n=282$). Multivariate regression models were used to identify predictors of early biochemical remission (12 weeks-1 year postoperatively) according to the 2010 consensus criteria, long-term clinical remission (no additional treatment applied at last follow-up) and relative GH and IGF-1 reduction.
Results
The presence of a macroadenoma (vs. microadenoma, OR = 0.17, [0.09 – 0.34], $P \leq 0.0001$) was associated with a lower chance of early biochemical remission. A lower random GH concentration at diagnosis (OR = 0.98, [0.97 – 0.99], $P = 0.0058$) was associated with a higher chance of long-term clinical remission, while cavernous sinus invasion (OR = 0.35, [0.16 – 0.77], $P = 0.0097$) and the presence of a macroadenoma (OR = 0.43, [0.20 – 0.93], $P = 0.0321$) were associated with a lower chance of long-term clinical remission. Higher GH and IGF-1 concentration at diagnosis were associated with more relative IGF-1 reduction (ß = 8.90, SE = 1.59, $P \leq 0.0001$; ß = –0.22, SE = 0.05, $P \leq 0.0001$, respectively).
Conclusion
Tumor size, GH concentration at diagnosis and cavernous sinus invasion are the best predictors for remission after transsphenoidal surgery in acromegaly.

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AEP661

Metyrapone treatment in endogenous Cushing's syndrome. Results from a prospective multicenter, open-label, phase III/IV study: Prompt

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Metyrapone treatment in endogenous Cushing's syndrome. Results from a prospective multicenter, open-label, phase III/IV study: PROMPT
Background
Metyrapone is a steroidogenesis inhibitor approved in Europe for the treatment of endogenous Cushing's syndrome (CS) based on observational retrospective studies published over more than 50 years. We present data from the first prospective study designed to confirm metyrapone efficacy and good tolerance in patients with CS.
Methods
This single arm, open-label, multicenter, international trial enrolled 50 patients with CS who had three baseline 24 hours urine free cortisol (UFC) values at least 50% above the upper limit of normal (ULN = 165 nmol/24 h). Metyrapone was titrated over 12 weeks (W12) to achieve normal urine (mean of 3 values, mUFC) and serum cortisol levels. Patients whose mUFC did not exceed 2.5-fold the ULN could enter a 6-month extension period. The primary efficacy endpoint was the proportion of patients with mUFC ≤ ULN at W12 assessed in a central laboratory using LC-MS/MS. The most important secondary endpoint was a mUFC decrease of ≥ 50% at W12.
Results
At baseline, mean age was 47 years, mean mUFC (s.d.) was 1042 (1337) nmol/24 h and median mUFC (range) was 570 (291–8476) nmol/24 h (3.5 × ULN). Diabetes mellitus (65%) and hypertension (51%) were the most common comorbidities at baseline. At W12: 48% (23 of 48 patients) met the primary endpoint. Another 40% (19 of 48 patients) had mUFC ≤ 2 × ULN at W12. Median percentage decrease in mUFC from baseline to W12 was –74%. Secondary endpoint was met by 81% of patients who had a mUFC decrease of 50%. Final median metyrapone dose was 1500 (250; 5500) mg/day at W12. At W12, circulating cholesterol, HbA1C and fasting glucose improved with mean decrease of 12%, 3% and 6% respectively and median systolic and diastolic blood pressure also decreased by 3.4 and 3.5 mmHg respectively. At W12, ACTH increased 20% (+ 9 ng/l) from baseline. Twenty six (52%) patients experienced mild to moderate related adverse events (AEs). One patient discontinued before W12 because of an unrelated SAE on day 2 (pneumonia with septic shock). The most common AEs were nausea (24%), decreased appetite (18%), fatigue (14%), headache (10%), peripheral edema (6.0%), hypokalemia (6.0%) and hypertension (6.0%). Reversible adrenal insufficiency occurred in 6 (12%) patients.
Conclusions
This prospective study in patients with CS confirms that metyrapone effectively lowers UFC levels with a tolerability profile similar to the previously reported safety profile.

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AEP662

Predictors of response to medical therapy with pegvisomant and pasireotide lar in SRLs-resistant acromegaly

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Background
Pegvisomant(PegV) and Pasireotide LAR(Pasi) are commonly used in acromegaly patients resistant to first-generation SRLs. Predictors of response to therapy with PegV and Pasi in this subset of patients are still unclear. These findings may be useful in choosing the most appropriate therapeutic option for the personalized treatment of patients affected by more aggressive disease. We aimed to identify individual predictors of responses.
Methods
We conducted a longitudinal retrospective cross-sectional study in a multicenter study on 64 acromegaly patients resistant to first-generation SRLs. We enrolled in the study patients (1) who underwent surgical resection as first-line therapeutic option, (2) defined resistant to adjuvant treatment first-generation SRL at high dose, after at least 6 consecutive months of therapy, (3) treated with Pasi or PegV for at least 6 months. Patients treated with radiotherapy in the previous 10 years were excluded. Biochemical control was defined as normal IGF-I.
Results
51 patients were treated with PegV and 31 with Pasi. 57 patients were female. Mean age was 37.5 months (SDS: 13.4). Mean IGF-I×ULN at study entry was 3.4 (SDS: 1,1). The clinical, biochemical and morphological features was similar between the two groups. In the Pasi-treatment group, 18 patients were switched from PegV (15 as not-controlled and 3 for intolerance).Of the 51 patients treated with PegV, biochemical control was obtained in 36 (70.6%) and among the 31 patients treated with Pasi, biochemical control was obtained in 20 (64.5%). In the PegV-treatment group, patients resistant totherapy showed significantly higher Ki67 compared to the responding patients ($P=0.04$), a more frequent invasion of the ventricular system ($P=0.006$), and higher values of IGF-I×ULN before treatment ($P=0.01$). In the Pasi-treatment group, patients resistant to therapy showed significantly higher Ki67 compared to responders ($P=0.001$), higher IGF-I×ULN before treatment ($P=0.04$), a higher prevalence of d3-isoform of the GH receptor ($P=0.04$) and a low/absent expression of subtype 5 of somatostatin receptors ($P=0.04$). The SSTR2A expression was similar between the two groups of treatment ($P=0.06$).
Conclusions
Our data confirm in real life scenario the efficacy of Pegvisomant and Pasireotide LAR in obtainingbiochemical control of acromegaly in patients affected by more aggressive disease and suggest that molecular markers may be useful for optimizing an individualized treatment outcome.

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AEP663

Efficacy of monotherapy versus combined GH receptor antagonist therapy in patients with somatostatin receptor analogues resistant acromegaly

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Background and Aims
GH receptor antagonist (Pegvisomant –PEG) has been shown to obtain IGF1 normalization in 60–90% of patients with acromegaly in clinical trials. The aim of the study is to evaluate real life response and side effects of PEG treatment in monotherapy versus combined with somatostatin analogues and/or cabergoline in patients with somatostatin analogues resistant acromegaly.
Methods
We included 40 patients (22F/18 M) consecutively evaluated between Jan2001-Dec2019. Baseline and at 6 months, and then yearly till 10 years serum IGF1, glucose, hepatic enzymes and tumor diameters were recorded.
Results
All patients were previously operated and 26 were irradiated. There were 9 patients treated with PEGmonotherapy (highest dose 136.11±61.93 mg/week) and 31 patients received combination therapy (highest PEG dose 81.93±42.30 mg/week). IGF1 levels were lowered after 6 months and 1year of treatment and then remained stable till 10 years of treatment with PEG (from 2.27±0.18 ×ULN to 1.86±0.16 and 1.35±0.13 xULN at baseline, 6 months and 1 year, respectively, $P=0.012$ baseline versus 6 months and <0.001 baseline versus 1 year; 0.001 1 year vs 6 months). We obtained control of acromegaly in 20% of patients at 6 months, and in 42% and 58.3% after 1 and 3 years. There were no hepatic adverse reactions and tumor diameters nonsignificantly raised from 15.76±2.18 mm at baseline to 20.36±2.99 mm at 6 months, 18.43±3.62 mm at 1 year and 24.96±67 mm at 4 years ($n=6$). In patients treated by monotherapy, glucose level were lower at 6 months versus baseline (88.61±19.68 and 101.96±16.49 mg/dl, respectively, $P=0.01$). Patients treated by monotherapy were more frequently controlled (8/9; 88.88%) than patients treated with combination (12/31; 38.70%), $P=0.01$.
Conclusion
After 3 years of treatment with pevisomant, more than 50% of patients with somatostatin analogues resistant acromegaly were controlled. Patients treated with monotherapy were more frequently controlled and had better glucose control.

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AEP664

The role of repeated prolactin samples in patients with hyperprolactinaemia

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Introduction
Current guidelines recommend a single prolactin sampling for the diagnosis of hyperprolactinaemia. Nonetheless, in some patients, prolactin levels may normalize in a subsequent sampling or if prolactin is collected through a venous catheter some time after puncture. We aimed to assess the percentage of patients in which prolactin remained elevated in repeated sampling and to determine the best prolactin cutoff associated with persistent hyperprolactinaemia.
Methods
We retrospectively studied patients referred to the endocrinology clinic of the Centro Hospitalar do Tâmega e Sousa from 2006 to 2019 due to hyperprolactinaemia (referral prolactin – rPRL). We included those that underwent repeated prolactin samples by a peripheral venous catheter. The first sample (PRL0') was collected immediately after catheter insertion, the second sample 20 – 30 min after catheter insertion and the third sample 40 – 60 min after. The lowest value of these last two samples was defined as the nadir prolactin (nPRL). Prolactin was considered normal if within the reference range for sex and menopausal status. We excluded patients treated with dopamine receptor agonists. The endpoint under analysis was persistently elevated PRL0' and nPRL. Receiver-operating characteristic (ROC) curves were used to determine the best rPRL cutoffs to predict elevated PRL0' and nPRL. A logistic regression analysis was used to test the association between the rPRL cutoffs and persistent hyperprolactinaemia.
Results
We studied 53 patients (three males), mean age 34±3 years, and 51.0% treated with possible hyperprolactinemic drugs. Median rPRL: 48.0 ng/ml (39.5 – 72.5), PRL0': 34.3 ng/ml (18.0 – 50.8) and nPRL: 29.5 ng/ml (11.4 – 44.4). PRL0' was elevated in 35 (66.0%) patients and in 7 of them a normal nPRL was reached; therefore 28 (52.8%) patients presented persistent hyperprolactinaemia. The areas under de ROC curves for the association between rPRL and elevated PRL0' and nPRL was 0.70 (95% CI : 0.56–0.85) and 0.70 (95% CI : 0.56 – 0.84), respectively. The best cutoff for elevated PRL0' was 53.4 ng/ml: 51.4% sensitivity, 88.9% specificity, 83.8% positive predictive value (PPV) and 62.0% negative predictive value (NPV). The best cutoff was the same for elevated nPRL prediction: sensitivity=53.6%, specificity=80.0%, PPV=75.0% and NPV=60.6%. Patients with rPRL>53.4 ng/ml had an OR of elevated PRL0' and nPRL of 5.29 (95% IC: 1.30–21.59, $P=0.02$) and 3.65 (95% CI : 1.12 –11.90, $P=0.03$), respectively.
Conclusions
Approximately half of the patients referred due to hyperprolactinaemia reach normal levels in repeated sampling. Patients with prolactin>53.4 ng/ml (2 times the upper reference level) have 80% probability of having real hyperprolactinaemia.

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AEP665

Assessment of disease control in patients with acromegaly treated with long-acting somatostatin analogs (SMSa) varies according to the time when IGF-I levels are measured during the month following the injection

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Introduction
Acromegaly is associated with multiple comorbidities and excess mortality. However, disease burden is reduced by maintaining IGF-1 (and/or GH) levels under safe levels. First generation long-acting SMSa, administered at monthly intervals, represent the first line medical treatment. According to guidelines, its efficacy is evaluated through IGF-I measurements. However, there are no data indicating the optimal time for measuring IGF-I levels after the SMSa injection, and if the interval between the injections and the blood sampling might have importance for assessing the disease control.
Aim
To determine in real life if the time when IGF-I is measured after SMSa injection provides a consistent and correct evaluation of disease control in order to improve understanding of patients' response to chronic treatment and to set up a more pertinent follow-up program.
Methods
Retrospective analysis of four (to five) weekly blood sampling performed for IGF-I measurement in 35 patients (males, 49%; mean age, 60±14 years) with acromegaly treated with long-acting SMSa (octreotide LAR, $n=9$; lanreotide Autogel, $n=26$) for a mean duration of 9.4±8.9 years. Blood was sampled according to the following schedule: just before the SMSa injection and then one, two, three, and eventually four weeks after the injection (the fourth sampling being made just before the next injection). IGF-I was also measured weekly in six healthy controls (mean age, 40±11 years) for four weeks. Data were analyzed through charts, t-test and repeated measures ANOVA test.
Results
According to IGF-I levels, acromegaly was considered as controlled in 58.8%, 73.5%, 71.9% and 64.7% of patients before injection, at the first, second and third week following the injection, respectively. Only 58.8% of patients had normal IGF-I during the entire follow-up. Repeated measures ANOVA test showed statistically significant difference between the four measures ($P=0.005$). Reproducibility between IGF-I levels measured just before the injection (first sampling) and four weeks later, just before the next injection, was good (two-sided t-test, $P=0.29$). IGF-I variability in uncontrolled patients was higher than that of healthy controls.
Conclusion
Our study highlights that evaluation of disease control in patients on long-acting SMSa may vary according to the time when IGF-I is measured after the injection. According to our study, a single random IGF-I measurement does not properly reflect monthly hormone profile in 41.2% of our patients. If IGF-I is measured one week after the injection more patients are considered as controlled than when IGF-I is measured later between monthly injections.

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AEP666

Surgical and clinical outcome in elderly patients affected by non-functional pituitary adenoma treated by endoscopic transnasal transsphenoidal surgery: A monocentric study

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The rate of diagnosis of pituitary adenomas in the elderly is increasing, as a consequence of the improved life expectancy. The management of elderly patients affected by pituitary adenomas are still a subject of debate in literature. In particular, data on the safety of endoscopic transnasal transsphenoidal surgery (TNS) are still controversial. The primary endpoint of the present study is to assess the surgical outcome of a cohort of patients who underwent TNS for non-functional pituitary adenoma (NFPA). The secondary endpoint is to evaluate their endocrinological post-TNS outcome and to compare the results with those of a younger control group. Between 2012 and 2019, 353 patients with NFPA underwent TNS-surgery atour Pituitary Centre;among them, only the 188 patients with a complete clinical, hormonal and radiological baseline evaluation and at least one complete post-TNS evaluation were selected. The average follow-up period was 52 months (range 6 – 210). Patients were divided in two groups, depending on their age at surgery (group 1: patients ≥70 years-old; group 2: patients <70 years-old). Data about endocrinological and surgical outcome from the two groups were compared by Pearson's chi-square test. Forty-three percent of the 188 patients enclosed in the study were ≥70 years-old [group 1; mean age 74.3, range 70 – 84], while 57% ($n=107$) were <70 years-old [group 2; mean age 50.9, range 21 – 68]. At the first evaluation, visual defects were more common in group 1 (61.7% vs 44.3%; $P=0.03$), while headache was predominant in group 2 (36.8% vs 16%; $P=0.002$). No significant differences in either pre-TNS surgery pituitary deficits presence or the specific type of hormonal deficits were found between the two groups. Similarly, group 1 and group 2 did not differ in surgical complications rate, the onset of novel post-TNS pituitary deficits, visual field normalization rate, and remission rate. After surgery, a higher recovery rate of pre-existing pituitary deficits was observed in group 2 patients (32.4% vs 6.3%, $P=0.000$). In particular, we observed a higher frequency of both gonadal function and GH secretion in group 2 patients (15.8% vs 1.3%, $P=0.001$ and 6.34% vs 0%, $P=0.03$ respectively). In conclusion, age should not be considered as a predictive factor of surgical complications or worse endocrinological outcome, even if it seems to be associated with a poorer recovery of pre-TNS pituitary deficits.

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AEP667

Gender differences in airway obstruction in men and women with acromegaly: A longitudinal study

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Introduction
Acromegaly is a slowly progressing systemic disease that leads to numerous changes in metabolism and organ function. A large cross-sectional study showed signs of subclinical airway obstruction in female patients. We performed a longitudinal study of lung function testing to compare parameters of airway obstruction in male and female patients with acromegaly over time.
Methods
40 patients with acromegaly (24 male, 16 female) underwent repeat lung function testing with a mean interval of 10.1±4.3 years. Lung function parameters were converted to percentages of predicted values obtained from normative data to correct differences of absolute values for age, sex, height and weight. We investigated the impact of disease activity on changes of airway obstruction by categorizing patients as biochemically controlled if at the date of repeat testing random growth hormone levels were below ng/ml and IGF-I levels within the age and sex reference range of the assay used. We calculated group comparisons using an independent samples t-test with a significance threshold of 0.05 and interpreting p values below 0.1 as trend.
Results
While FEV_1, FEF_{75}, FEF_{50}, and FEF_{25} did not differ significantly between male and female patients over time, we found a significant increase of total specific resistance in women (sR_{tot}: $P=0.014$; men – 5.0%, women +30.2%). Furthermore, in women there is a trend for increased total airway resistance (R_{tot}: $P=0.078$; men –3.6%, women +17.2%) as well as decreased peak expiratory flow (PEF; $P=0.096$; men+5.5%, women –10.4%). Changes in airway obstruction were unrelated to biochemical control of acromegaly.
Conclusion
Female patients with acromegaly seem to develop airway obstruction over time, regardless of disease activity. The mechanism of this change remains to be elucidated.

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AEP668

Withdrawal from long-acting somatostatin receptor ligand injections in adult patients with acromegaly: Results from the phase 3, randomized, double-blind, placebo-controlled optimal study

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Background
Data on the impact of withdrawal from long-acting somatostatin receptor ligand (SRL) injections on disease activity in patients with acromegaly are limited. The CHIASMA OPTIMAL study assessed the efficacy and safety of oral octreotide capsules (OOC) in adult patients with acromegaly responding to SRL injections. The placebo arm of this study allowed for assessment of acromegaly activity in patients after withdrawal from SRL treatment.
Methods
A multinational, randomized, placebo-controlled study was conducted in 56 adult patients with active acromegaly. Patients had evidence of active disease (IGF-I≥1.3 × ULN after last pituitary surgery) and an average IGF-I≤1.0 × ULN on a stable dose of SRL injection (≥3 months). Patients were randomized 1 month after last injection to OOC or placebo for 36 weeks, with an optional open-label extension (OLE). The primary aim was to determine the proportion of patients maintaining biochemical response (IGF-I≤1.0 × ULN; average, week 34 and 36).
Results
The trial met the primary endpoint, with 58% (16/28) of patients receiving OOC maintaining IGF-I response vs 19% (5/28) receiving placebo ($P=0.008$). The median time to loss of response (2 criteria evaluated: IGF-I>1.0 and ≥1.3 × ULN) was 16 weeks in the placebo group; while not reached in the OOC group. Of the 5 patients in the placebo group who maintained their biochemical response at 36 weeks, only 2 did not meet loss of response criteria. When IGF-I values for any 2 consecutive visits were analyzed for patients receiving placebo, 93% (26/28) lost response based on IGF-I>1 × ULN and 79% (22/28) lost response based on IGF-I≥1.3 × ULN. Irrespective of biochemical control of acromegaly, 26/28 patients receiving placebo experienced active disease-related symptoms reported as AEs of special interest (AESIs). Most common AESIs (≥5%) included arthralgia/arthritis (60.7%), soft tissue swelling (35.7%), headache (32.1%), hyperhidrosis (25%), carpal tunnel (14.3%), musculoskeletal pain (14.3%), weight increased (7.1%) and tongue disorders (7.1%). The 5 patients receiving placebo with controlled IGF-I at 36 weeks received active treatment in the OLE by decision of study PIs, as they were deemed to have either lost their response during the study or had active acromegaly symptoms.
Conclusion
93% of patients receiving placebo lost response following withdrawal of injectable SRLs, with a median duration of 16 weeks. All 5 patients receiving placebo who met the primary endpoint criteria at the end of the study were assessed clinically to have active disease and received OOC treatment in the OLE.

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AEP669

Impact of imputation method on efficacy results from the phase 3 optimal study of oral octreotide capsules in adult patients with acromegaly

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Objective
The phase 3 CHIASMA OPTIMAL study assessed efficacy and safety of oral octreotide capsules (OOC) in patients with acromegaly controlled on injectable somatostatin receptor ligands (SRLs). Sensitivity analyses were conducted for efficacy endpoints using two methods of imputation (i.e., the process of replacing clinical data with substitution values) to address missing data points due to some subjects reverting back to their prior injectable SRL treatment.
Methods
Patients were ≥18 years of age and had evidence of active acromegaly with an average IGF-I≤1.0 × ULN (utilizing the IDS iSYS assay calibrated to WHO recombinant reference standard 02/254). At baseline, patients were randomized to receive OOC or placebo for 36 weeks. The primary endpoint waspproportion of patients maintaining biochemical response, defined as IGF-I≤1.0 × ULN (2-value average at weeks 34 and 36) (Samson *et al.* ENDO 2020). Per study protocol, patient study discontinuations were considered non-responders regardless of clinical response at the time of discontinuation (non-response imputation). Additional exploratory analyses were performed utilizing the last observation carried forward (LOCF) analysis, as well as a completers analysis of response among the subgroup that completed the entire 36 weeks on study drug. The response rates reported for the primary end point are slightly adjusted for stratification differences as prespecified in the statistical analysis plan.
Results
Twenty-eight patients received OOC and 12 failed to maintain biochemical response based on the primary endpoint. Seven of these 12 patients discontinued treatment early – 5 due to treatment failure and 2 due to AEs. The remaining 5 patients completed the 36-week protocol on study drug. Of these 5 patients, 4 had IGF-I values between >1.0 and ≤1.3 × ULN and 1 completed the study with an IGF-I of 1.7 × ULN with no clinical symptoms. 58.2% of patients in the OOC group met the primary endpoint of maintenance of biochemical response at the end of study using the non-response imputation. Using LOCF imputation, 64.3% (18/28) of patients met this endpoint. Of those completing the study ($n=21$), 76.2% maintained response.
Conclusion
CHIASMA OPTIMAL primary endpoint was assessed using the non-response imputation for patients who discontinued treatment early, with a 58.2% response rate. However, when assessing the response rate based on LOCF imputation, or in study completers, similar to other phase 3 studies for acromegaly, the rate was imputed at 64.3% and 76.2%, respectively.

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AEP670

Eucaloric very low-carbohydrate ketogenic diet as a new supportive treatment modality for acromegaly?

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Objective
Acromegaly is caused by a growth hormone (GH)-secreting pituitary tumor and its signs are linked to increasedGH-dependent hepatic insulin-like growth factor I (IGF-I) synthesis. A eucaloric very low-carbohydrate ketogenic diet (euVLCK;<50 g/day) induces ketosis and reduces portal insulin concentrations, which down-regulate hepatic GH receptors and reduce IGF-I synthesis. Somatostatin receptor ligands (SRLs) reduce GH secretion by the pituitary tumor,resulting in IGF-I normalization in about 50% of patients. Remaining patients should switch to (or add) the expensive drug pegvisomant (PEGV). Our concept is that in acromegaly a euVLCK diet exerts insulin-induced IGF-I normalization without the unwanted increase in GH, as the GH-inhibiting SRL therapy is continued.
Method
We performed a proof-of-concept study ($n=11$, six females) to determine whether a 2-week euVLCK diet (35 g carbohydrate, 155 g fat and 115 g protein/day) as adjuvant to first-generation SRLs reduces IGF-I concentrations in uncontrolled acromegaly patients.

Results
During the euVLCK diet, mean carbohydrate intake decreased from 194.4 [s.d. 143.1] gramsto 32.6 [14.7]. IGF-I concentrations decreasedsignificantly (median 0.83 [IQR 0.62 – 0.91] ULN vs 1.10 [1.02 –1.25], $P=0.014$) and normalized in all but one patient, without the concomitant increase in GH (median 1.9 [IQR 0.4–3.7] µg/l vs 2.0 [0.7 – 3.6], $P=1.00$). This patientstill showed substantial decrease in GH after the euVLCK diet and presented with the highest degree of insulin resistance. Overall, HbA1c decreased slightly(mean 38.6 [s.d. 4.4] mmol/mol vs 39.8 [5.2], $P=0.028$). Insulin resistance, lipids and body composition did not change significantly. Although the diet was eucaloric, mean body weight decreased by about 1 kg. Of note, weight loss was not associated with changes in IGF-I concentrations ($r_s=-0.24$, $P=0.47$).Overall, the diet was well tolerated and all patients completed the study. Interestingly, SRL dose reduction was warranted in three out of six patients continuing a low-carbohydrate ketogenic diet (80 g/day; median 0.83 [IQR 0.75 – 1.01] ULN after median 3.0 months) as adjuvant to their initial SRL therapy.
Conclusion
This proof-of-concept study illustrates the ability of an adjuvant euVLCK diet to achieve control of IGF-I without affecting GH concentrations in acromegaly patients uncontrolled with first-generation SRLs. Our results could affect the clinical management of acromegaly as a euVLCK diet might deploy as an effective adjuvant treatment in some patientsbefore initiating PEGV treatment. Additional studies are needed to evaluate long-term safety and efficacy of and compliance with an euVLCK diet.

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AEP671

To score or not to score? Is Ki-67 analysis worthwhile in pituitary neuroendocrine tumours?

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Pituitary neuroendocrine tumours (PitNETs) are heterogeneous and have limited biomarkers to predict their behaviour, thus making their prognostication difficult. Ki-67 is a protein expressed in active phases of the cell cycle and is one of the biomarkers utilized in routine assessment of PitNET tissue. Current European Society of Endocrinology recommendations advise that histopathological analysis of PitNETs should as a minimum include Ki-67 proliferation index and anterior pituitary hormones. In addition, when Ki-67 index is≥3%, p53 immunodetection and mitotic count should be undertaken. In order to obtain accurate Ki-67 assessment, manual counts of 1000 cells should be completed, which demands significant time and may be open to subjectivity. In addition, Ki-67 thresholds vary across studies and there has been debate about the proposed cut-off value of 3%. There are no internationally agreed guidelines for modern image analysis approaches in PitNETs. A retrospective assessment of Ki-67 index was piloted in 30 PitNETs of varying cell types using QuPath digital image analysis software. Digital cell counts of Ki67 index were undertaken in 1000 cells and 10,000 cells for comparative purposes. Average Ki-67 index per 10,000 cell count was 1.12% and per 1000 cell count it was 1.17%. Diagnostic reports of the 30 tumour samples identified three tumours with increased Ki-67 index. Digital image analysis of these three samples identified one of these as having a Ki-56 index≥3%, while the other two had Ki-67 index<3% on both 10,000 and 1000 cell counts. In addition, digital image analysis also identified a further sample with Ki-67 index≥3% which was not originally reported as elevated. When appropriate detection thresholds are defined, QuPath digital analysis software identifies PitNET cells and Ki-67 positive cells. QuPath also facilitates assessment of Ki-67 in larger numbers of tumour cells which may provide a better representation of whole tumour Ki-67 expression. A further 200 tumour slides will be analyzed and presented alongside the 30 samples in this pilot study. In conclusion, this pilot study demonstrates QuPath is a reliable method to score Ki-67 index in PitNETs.

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AEP672

Giant prolactinomas: Is it possible to stop treatment?

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Giant prolactinomas are tumors with a large size >4 cm and/or prolactin levels higher than 3000 ng/ml and/or highly invasive growth. Today dopamine agonists (DA), mainly cabergoline (CAB), are the first-line choice in the treatment of these tumors
To assess the efficacy, safety and long-term follow-up of patients with giant prolactinomas treated with DA. We retrospectively reviewed the clinical records of 33 patients with giant prolactinomas. Mean age at diagnosis was 39.5±18.5 years, 73% men. The median follow-up time was 6.6 years (2.5 – 9.6). At diagnosis, median prolactin (PRL) level was 4.700 ng/ml (3.131 – 10.900), mean maximum diameter of the tumors was 4.77±1.15 cm; headaches were present in 58%, hypogonadism in 79%; 85% had invasive tumors, 82% had visual field (VF) impairment. Since diagnosis, almost all patients were treated with CAB except 2, who were started on bromocriptine, both were switched to CAB afterwards. Results: 64% of patients normalized PRL levels (median time of 6 months) with a mean dose of 1.66±1.49 mg/week of CAB. Fifty-three percent of patients reached this prolactin nadir in 2–4 months with a maximum dose <2 mg/week. Median PRL level in the last visit: 34.78 ng/ml. Ninety-four percent of patients decreased PRL level during follow-up: 48% normalized PRL, 13% remained with mild hyperprolactinemia, 39% with significant hyperprolactinemia. Eighty-five percent of tumors reduced volume, 36% evolved to empty sella, the remaining tumors achieved a mean decrease 1.48 cm compared to initial size (69% average reduction compared to the initial diameter). VF remained normal in patients in whom it was not affected, in the patients who presented VF involvement: 42% improved, 49% remained unchanged, 9% worsened. Complications during follow-up: Cerebrospinal fluid leak 3 patients, chiasmatic ptosis 1, intra-tumoral hemorrhage 1. In follow-up, 5 patients required surgery; 5 patients died, 3 because of the tumor. In 4 patients CAB was stopped between 48–264 months after initiating treatment, but in all of them CAB was reinitiated due to symptomatic hyperprolactinemia, in 28 patients treatment was never discontinued.
Conclusions
With low-moderate does of CAB and very few complications, CAB was effective in treatment of giant prolactinomas reducing tumor size (some of them evolved to empty sella) and normalizing PRL levels in almost half of our patients. In our experience of 25 years of follow-up we have not had any patients without treatment.

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AEP673

Development of a local reference range for hypertonic saline-stimulated copeptin

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Hypertonic saline stimulated copeptin measurements have recently been described for the diagnosis of central DI. A copeptin cut-off of >4.9 pmol/l has a diagnostic accuracy of 96.5% for distinguishing primary polydipsia from central DI[1]. A copeptin assay has recently been established in our laboratory. Validation of hypertonic saline-stimulated copeptin concentrations in our local population is needed before this test can be used with confidence in patients presenting to our institution with polyuria-polydipsia syndrome. The aim of this study was to develop a local reference range for hypertonic saline-stimulated copeptin in healthy volunteers. Twenty healthy volunteers (10 male and 10 female) were recruited. Subjects underwent a hypertonic saline test, as previously described (3). Hypertonic saline (3%) was administered as an initial 250 ml bolus followed by 0.15 ml/kg/minute until a target serum sodium of ≥150 mmol/l was reached. At this time, blood was drawn for copeptin measurement.

Median age was 28.5 years (range 25 – 50); median body weight was 75.05 kg (range 50.4 – 106); median baseline plasma sodium was 138 mmol/l (range 135 – 143) and median serum osmolality was 291.5 (range 281 – 297). Median peak sodium was 152 mmol/l (range 150-154) with osmolality 314.5 mmol/kg (range 306 – 320). Median volume of hypertonic saline infused was 1536 ml (1230 – 2220 ml) and median hypertonic saline stimulated copeptin was 33.8 pmol/l (9.6 – 167.4). Overall symptom burden was 6/10 (range 3/10 – 9/10). 10 patients' experienced nausea and 3 patients experienced vomiting. Copeptin was significantly higher in those who experienced nausea (35.4 pmol/l; range 30.2 – 82.3 pmol/l) and those who experienced vomiting (91.6 pmol/l; range 58.9 – 95.5 pmol/l) compared to those patients who did not experience either (19.7 pmol/l; 13.0 – 30.9 pmol/l) ($P=0.0465$ and $P=0.0085$ respectively). There were no serious adverse events.
Nausea and/or vomiting were associated with significantly higher copeptin levels. Development of a local reference range for hypertonic saline stimulated copeptin measurements will assist in interpretation of the test in our local population of patients presenting with polyuria-polydipsia syndrome.
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AEP674

A key role for conservative treatment in the management of pituitary apoplexy

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Objective
The management of pituitary apoplexy, a rare emergency neuroendocrine condition, is controversial. The aim of the present study was to compare the outcome of patients with pituitary apoplexy managed either by a conservative or surgical approach.
Methods
A retrospective cohort study including patients diagnosed between 2007 and 2018 in a tertiary French university hospital. Pituitary apoplexy score was retrospectively applied in a perspective of therapeutic decision support.
Results
Forty-six patients were treated for a pituitary apoplexy either with conservative management ($n=27$) or surgery ($n=19$). At initial evaluation, visual field defects and visual acuity impairments were more frequent in patients from the surgery group. At one year there were no statistical differences in the rates of complete/near-complete resolution of visual field defects (100% vs 91.7%), visual acuity impairment (100% vs 87.5%) and cranial nerve palsies (83.3% vs 100%), between conservative and surgical treatment groups. Endocrine function prognosis was poor regardless of the treatment. Pituitary apoplexy score ($n=42$) was at 3.4 on average in the early surgery group and 1.4 in the conservative treatment/delayed surgery group. Among patients with a score <4, 31.3% were operated at first line and did not present better outcomes than patients managed conservatively. 80% of patients with a score ≥4 underwent surgery.
Conclusions
Pituitary apoplexy score may be a reliable parameter for defining therapeutic strategy. Patients with non-severe and non-progressive neuro-ophthalmological deficits can be managed conservatively without negative impact on outcomes, thus surgery should be reserved foronly those patients with a Pituitary apoplexy score ≥4.

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AEP675

Gender dimorphism of intramuscular fatty infiltration and related muscle dysfunction in patients with long-term control of acromegaly

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Background
Muscle weakness persists in patients with acromegaly (ACRO) even long-term after disease control. Mechanisms determining this sustained impairment are not known. We hypothesized that alteration of muscle architecture, due to intramuscular fatty infiltration, is associated with muscle dysfunction in these patients.
Patients and methods
Thirty-seven acromegalic patients [21 females and 16 males, mean (± S.D.) age, 53±9 years, BMI, 27±4 kg/m^2 and duration of control, 92±58 months], and 37 age, gender and BMI-matched controls were studied. The degree of fatty infiltration (FF, fat fraction) in the thigh muscles was measured using magnetic resonance imaging (MRI), 2-point Dixon sequence in the anterior, posterior, and combined anterior and posterior compartments, rectus femoris and vastus intermedius. The following muscle function tests were also performed: Gait Speed Velocity (GS), Timed Up and Go (TUG), 30-Second Chair Stand and Hand Grip Strength.
Results
Mean FF (%) in all the compartments analysed was increased in patients as compared with controls ($P<0.01$ for all the comparisons). ACRO female patients had greatermean FF in the anterior (29.2±6.8% vs 20.5%±3.9%, $P<0.01$), posterior (38%±8.4% vs 27%±5%, $P<0.01$), combined anterior and posterior compartments (33.7%±7% vs 23.7%±4%, $P<0.01$),rectus femoris (28.9%±8% vs 16.9%±4.9, $P<0.01$) and vastus intermedius (21.3%±5.6 vs 14.9%±2%, $P<0.01$), as compared with males. Gait speed was slower in ACRO patients as compared with controls (1.18±0.2 vs 1.33±0.2 $P<0.05$). Performance on TUG was worse in ACRO women as compared with ACRO men (6.5±1.1 vs 5.5±1 for TUG; $P<0.05$). Greater mean intramuscular FF in all the compartments analysed was associated with worse performance on TUG ($P<0.01$), in patients only. Muscle mass and intramuscular FF in both posterior and combined anterior and posterior compartments were associated with IGF-I SDS in ACRO men only ($r=0.49$ and $r=0.54$, $P<0.05$ for both correlations). Thirty-second chair stand was negatively associated with GH in ACRO men only ($P<0.05$). In a multiple linear regression model, female gender and older age predicted intramuscular FF in the combined anterior and posterior compartment ($\beta=0.49$; $P<0.05$), in ACRO patients. Intramuscular FF of the combined anterior and posterior compartments predicted the performance on TUG after adjusting for gender and age ($\beta=0.75$, $P<0.01$) in ACRO. Conclusions: Intramuscular fatty infiltration is increased in ACRO patients with long-term control of the disease, especially in females. ACRO females also present with poorer muscle function than males. Intramuscular fat accumulation may be one of the mechanisms underlying sustained muscle weakness in acromegaly.

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European Society of Endocrinology audit and multi-country comparison of Adult Growth Hormone Deficiency (AGHD) treatment in clinical practice in Europe and Australia; –how closely are protocols and best practice recommendations followed

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Background
Current guidelines recommend that susceptible patients should be tested and treated for AGHD. Still, it is not universally recognised as a distinct entity and reimbursement of GH replacement therapy is not available in some countries.
Aim
1) to record current practice of AGHD management throughout Europe and benchmark it against existing guidelines, 2) to evaluate educational status of health care professionals.
Patients and methods
Practicing endocrinologists were encouraged by ESE to complete an electronic questionnaire with aggregated data of AGHD patients diagnosed and/or treated in 2017–2018.
Results
Twenty-nine centres from 17 European countries and one from Australia participated with 2148 AGHD patients including 30% of childhood onset. The aetiology included non-functioning pituitary adenoma (26%), craniopharyngioma (14%) and genetic/congenital mid-line malformations (14%). Centres reported a maximum of 254 and a minimum of 9 patients, of which 71% were treated with GH. The percentage of treated patients ranged from 100% to 0 in countries, where GH treatment was not publically reimbursed at study entry; however, variability was observed between centres within the same country. Eighty-four percent of GH treatments were still on-going at the end of the study period. The main reasons for interruption were adverse events (22%, in 37% due to new cancer or tumour recurrence), administrative reasons (13%), lack of compliance (12%) and lack of positive effect (11%). Low adherence to guidelines was observed in many countries regarding diagnostic tests, cut-off values for GH, treatment initiation and/or transitioning. In 64%, no quality-of-life (QoL) questionnaire was reported. Requirements for treatment initiation beyond a biochemical test included, in some centres, patient compliance (72%), impaired QoL (45%),severe fatigability (35%), central obesity (10%), and age <65 years (10%). A common major cause of dissatisfaction was low AGHD awareness by non-endocrine health care professionals, and extent and quality of post-graduate AGHD curriculum training.
Conclusion
Despite available guidelines on AGHD since 2007 recommending GH replacement in adult hypopituitary patients, there are still countries in Europe where AGHD substitution therapy is not reimbursed. Knowledge among professionals and health administrators of adult GHD should be improved in order to optimize care of adults with hypopituitarism and GHD.

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AEP677

Carpal tunnel syndrome is common in patients with undiagnosed acromegaly – a swedish nationwide study

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Background
Carpal tunnel syndrome (CTS) is common in patients with acromegaly, with a reported prevalence of 19–64%. We have studied CTS in a large national cohort of patients with acromegaly, and the temporal relationship between the diagnosis of the two diseases.
Methods
Retrospective nationwide cohort study including patients diagnosed with acromegaly in Sweden between 2005 and 2017. Patients with acromegaly were identified in the Swedish National Patient Registry. Diagnosis of CTS and its potential risk factors, such as diabetes mellitus and acromegaly treatments were collected from the Swedish National Health Registries from 8.5 years before the diagnosis of acromegaly until death or end of the study. Standardized incidence ratio (SIRs) with 95% confidence intervals (CIs) were calculated with the Swedish population as reference. Cox regression models were used to identify potential risk factors for CTS in patients with acromegaly.
Results
The analysis included 556 patients with acromegaly (278 women, 50%), diagnosed at a mean age of 50±15 years. CTS was diagnosed in 48 (8.6%) patients, and 41 (7.4%) had been operated for CTS during the study period. SIR (95% CI) for CTS was 3.8 (2.8 – 5.0). The risk for CTS was similar for acromegaly patients with and without diabetes mellitus (SIR 3.5, 95% CI 1.6 – 6.7 vs SIR 3.9, 95% CI 2.7 – 5.3). Women with acromegaly had a higher risk (HR 2.5, 95% CI 1.3 – 4.7, $P=0.0038$) for CTS than men. CTS was diagnosed prior to acromegaly diagnosis in 42 out of 48 (88%) of the patients (median 3.1 years earlier, range 0.3 – 8.5 years). Thirty-five of 41 (85%) patients operated for CTS had undergone surgery before the diagnosis of acromegaly (median time 2.2 years, range 0.3 – 8.5 years).
Conclusion
Patients with acromegaly have a four times higher incidence of CTS compared to the general population. The vast majority of patients are diagnosed with CTS prior to acromegaly. The increased risk of CTS and the temporal relationship indicate a potential time-window for shortening the diagnostic delay in acromegaly by increasing the awareness of acromegaly in patients with CTS.

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AEP678

Levoketoconazole in the treatment of endogenous Cushing's syndrome: Extended evaluation phase results of the SONICS study

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Background
The phase 3, open-label SONICS study of levoketoconazole demonstrated sustained reduction in mean urinary free cortisol (mUFC) in adults with endogenous Cushing's syndrome (CS). The extended evaluation phase (Ext) of SONICS reported here further assessed long-term safety, tolerability, and benefit/risk of this treatment.
Methods
SONICS consisted of dose-titration (150 – 600 mg BID to attain maximally tolerated dose for mUFC normalization), 6-month maintenance, and 6-month Ext phases. Safety and efficacy evaluations occurred at Month 9 (M9) and Month 12 (M12) in Ext. Potential liver toxicity, QTc prolongation, and adrenal insufficiency were prespecified AEs of special interest. Exploratory efficacy assessments included mUFC response, changes in CS clinical signs and symptoms, quality-of-life (Cushing QoL score), and symptoms of depression (BDI-II score) from baseline to M9 and M12. Serum ACTH levels were assessed in those with Cushing's disease. The concentration-response relationship of levoketoconazole and mUFC levels was assessed. Treatment adherence was defined as ≥80–120% intake of the study drug.
Results
94 patients were enrolled and treated with ≥1 levoketoconazole dose; 77 patients entered and 61 completed the maintenance phase. 60 patients entered and 46 completed Ext. The most common incident AEs in Ext ($n=60$) were arthralgia (6.7%), headache (6.7%), hypokalemia (6.7%), QTc prolongation (6.7%), and nasopharyngitis (5.0%). AEs led to study discontinuation in Ext in 4 (6.7%) patients. No patients experienced increased ALT or AST>3 × ULN, had suspected adrenal insufficiency, or had QTcF interval of >460 msec in Ext. Serious AEs were reported in 4 patients during Ext, but none were considered levoketoconazole-related. 27 of 49 (55.1%) and 18 of 44 (40.9%) patients had normalized mUFC at M9 and M12, respectively. Concentration-response modeling indicated no evidence for tolerance to (ie, 'escape' from) mUFC reduction. Furthermore, mean ACTH levels at M9 and M12 were similar in those with ($n=15$) and without ($n=21$) mUFC normalization at M12. Treatment adherence was reduced at M12 (82.0%) relative to M9 (91.4%), likely accounting for the decreased mUFC normalization rate at M12. Mean improvements from baseline in CS clinical signs and

symptoms (acne, hirsutism, and peripheral oedema scores), and Cushing's QoL and BDI-II scores observed following 6 months of maintenance phase were generally maintained at M9 and M12.
Conclusions
In the SONICS study Ext, levoketoconazole was well tolerated with no new drug-related safety signals observed. Sustained mUFC response and improvements in CS clinical signs and symptoms, quality-of-life, and symptoms of depression were demonstrated in those completing Ext.

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Role of NGS in the diagnostic work-up of pituitary tumors and 'incidental findings'

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Background
Pituitary tumors are mostly sporadic, but in less than 5% of cases they can be associated to genetic syndromes, so harbouring germline mutations. Familial pituitary tumors are often more aggressive, so it's important to detect them, for both a better early diagnosis and genetic counselling. Before the development of Next-Generation Sequencing (NGS), Sanger sequencing was the most widely used method of DNA sequencing. Therefore, DNA samples were analysed following a phenotype-drivenstrategy, using direct sequencing of the coding regions of one single candidate gene at a time. Since 2000, the introduction of NGS, a massively parallel sequencing of millions of fragments of DNA, improved the accuracy of genetic testing with an overall reduction in time and costs. Consequently, genetic testing is more and more integrating into the clinical practice. In addition, some rare phenotypes are common to different clinical conditions caused by different genetic mutations. In this case NGS is useful to identify genotype-phenotype associations not recognized with single genes sequencing method, the so-called *'incidental findings'*.
Materials and methods
We carried out genetic testing in 25 patients (mean age 46.9), between November 2014 and September 2019. All patients received a diagnosis of pituitary tumor and were suspected to have a genetic syndrome according to the indications given by the literature. 14 patients were investigated for MEN-1 and 11 patients for FIPA. Gene analysis was performed with targeted NGS panel testing for the following genes: AIP, CDKN1b, CDC73, MEN-1, RET, PRKAR1A.
Results
2 patients had a mutation in AIP, thus confirming the suspected FIPA (2/11, 18%). 21 patients were negative for mutations in all the analysed genes. In one patient with suspected MEN-1, we unexpectedly found a heterozygosis mutation in exon 7 of *PRKAR1A* (well known as responsible for Carney Complex). The last patient, with a suspected MEN-1 too, had a heterozygosis mutation in the exon-intron junction of exon 2 of *CDKN1b* (responsible for MEN-4).
Conclusions
Our experience shows that the use of NGS should be now considered as an important step in the diagnostic work-up of pituitary tumors with suspected germline mutations. Moreover, massively parallel sequencing may lead to 'incidental findings', with clear implications not only inclinical practice but also for its consequent ethical issues.

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AEP680

fMRI for cognitive evaluation of adult survivors of childhood craniopharyngioma

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Introduction
The morbidity of craniopharyngioma (CP) includes cognitive dysfunction with attention deficits, impaired episodic memory and processing speed (Fjalldal *et al.*, 2013) and CP patients with hypothalamic damage are more affected. fMRI is a technique used to investigate cortical activity by detecting alterations in blood flow in response to stimuli or actions. Previously pre- and post-meal fMRI responses to visual food cues were investigated showing higher activation in patients with CP compared to controls (Christian *et al.*, 2012). Further, fMRI was used in an emotional face recognition task where neural activity revealed differential recruitment of fronto-limbic brain regions during recognition in patients with CP (Ozyurt *et al.*, 2014). The multi-source interference task is an fMRI paradigm that reliably activates the cingulo-fronto-parietal cognitive/attention network (Bush *et al.*, 2006). Our aim was to study activation in the cingulo-fronto-parietal cognitive/attention network using fMRI. We hypothesized that the patient group would demonstrate different cortical activation patterns compared to controls.
Methods
Included were 29 adult childhood craniopharyngioma patients (median age 36 [18–49] years) surgically treated, 13 with hypothalamic damage, and 15 without. Twenty-nine controls were matched for age, sex, and smoking habits. A gradient echo EPI sequence (TR/TE 1500/30 ms/ms) with a number of 25 slices, a number of 64 dynamics, and a voxel size of $3\times3\times4\,mm^3$ was used for the fMRI task. An additional MP-RAGE sequence (TR/TE 1900/2.54 ms/ms, $1\,mm^3$ isotropic resolution) was acquired to be able to perform the data analysis. The multi-source interference task was performed (Bush *et al.*, 2006). fMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Z (Gaussianised T/F) statistic images were thresholded non-parametrically using clusters determined by $Z>3.1$ and a (corrected) cluster significance threshold of $P=0.05$ (Woolrich *et al.*, 2001). Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann *et al.*, 2003).
Results
Activation maps demonstrate activation in expected areas (i.e. cingulo-fronto-parietal activation). No significant differences in activation was found between the patients gorup and controls.
Conclusion
In spite of well-known cognitive impairment in patients with CP we found no functional alterations in the cingulo-frontoparietal cognitive/attention network using fMRI.

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AEP681

Effects of long-term growth hormone replacemente therapy on body composition in adult patients with growth hormone deficiency

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Introduction
Growth hormone deficiency (GHD) is associated with worsening body composition and growth hormone replacement therapy (GHRT) has shown to improve it in several studies. The objectives of this study were to evaluate the effects of long-term GHRT on body composition in adult patients with GHD andassess, in this population, the agreement between two different methods to measure fat mass that are total body fat mass (FM) and relative fat mass (RFM).
Material and methods
We conducted a retrospective, longitudinal study in a cohort of patients with GHD under GHRT, followed in the Endocrinology and Nutrition Department of La Paz University Hospital. A total of 79 adult patients (46 women, 33 men), with mean age of 39.1 year-old at starting GHRT, were evaluated

for a mean time of 5 years (range 1 to 15 years). RFM, FM, body mass index (BMI) and waist-to-hip (W/H) ratio were measured at baseline and during follow-up, FM was measured by bioelectrical impedance analysis (BIA), RFM was calculated using a linear equation based on height-to-waist ratio proposed by Woolcott *et al.*, [Equation for women: 76–(20×(height/waist)); equation for men: 64–(20×(height/waist))]. The evolution of these parameters was assesed using ajusted generalized estimating equation models. The agreement between RFM and FM was estimated using the intraclass correlation coefficient (ICC).
Results
FM measured by BIA did not changesignificantly during the follow-up ($P=0.087$). RMF did not change the firsts years, but from the 3rd year of follow-up, it gradually increasedcompared to baseline (3rd year: OR=2.86; 95% CI=1.05–7.80; $P=0.04$. 4th year: OR=3.62; 95% CI=1.25–10.5; $P=0.02$. 5th year: OR=3.41 95%; 95% CI=1.32–8.8; $P=0.01$. 10th year: OR=5.56; 95% CI=2.19–14.5; $P=0.003$). After the 2nd year of therapy, BMI progressively increased (2nd year: OR=2.10; 95% CI=1.22–3.63; $P=0.008$. 3rd year: OR=2.19; CI 95%=1.18–4.07; $P=0.01$. 4th year: OR=2.30; 95% CI=1.02–5.17; $P=0.04$. 5th year: OR=2.84; 95% CI = 1.31–6.17; $P=0.008$. 10th year: OR=7.46; 95% CI=2.52–22.2; $P=0.0003$). W/H ratio did not change significantly ($P=0.06$). RFM showed good degree of agreement with FM measured by BIA (ICC 0.78, 95% CI=0.75–0.81).
Conclusions
1) In our population, we did not observe improvement in the anthropometric measures during GHRT. 2) RFM showed good agreement with FM measured by BIA, so it could be used to replace this technique when it is not avaliable.

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AEP682

Perception of stature and quality of life in young adult men referred for tall stature during adolescence. Perception of stature and quality of life in young adult men referred for tall stature during adolescence.

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Background and aims
Little is known about the long-term psychosocial effect of tallness and its treatment in male adolescents.[1] Therefore, psychosocial outcome, including adult coping with tall stature were investigated in young adult men, who had consulted for tall stature during adolescence.
Methods
All adult men (age >18 years) who had been referred for tall stature or rapid growth during adolescence (ages 11 to 16 years) between 2010 and 2013 in 3 Flemish University Hospitals and had bone age assessment, were invited to complete the SF36 instrument and a custom-made questionnaire. Relevant data were retrieved from their medical files.
Results
Of the 65 eligible subjects (having no underlying growth disorder and a normal mental development), 24 completed the psychosocial evaluation. Eight of them had been treated with high dose testosterone. Median (range) age was 20.5 (18 and 25) years and median self-reported height was 197 (185–207) cm. Current age and height were similar in the treated and untreated men, but predicted height was significantly higher in treated men (202.6 vs 198.9 cm, $P<0.05$). The ideal adult stature mentioned by participants was 190 cm. At adolescence respectively 88 and 75% and at adulthood respectively 63 and 88% of treated and untreated men reported to be satisfied with their stature. In total 75% of treated and untreated men were satisfied with the received recommendation to treat or not. Median scores on the eight SF36 subscales were similar between treated and untreated men, with the exception of a lower median score on general health perceptions in treated men. Median SF36 subscale scores were not significantly different from an age matched British control group, with the exception of higher scores on role limitations due to emotional problems in tall men. Positive perception of stature during adolescence was correlated with better scores on social functioning and bodily pain.
Conclusion
The majority of young men,being between 5–17 cm taller than the population mean, who participated in a psychosocial assessment, were satisfied with their current stature and previous decision to receive growth suppressive hormonal treatment or not. Previously treated men however, had a lower score on general health perceptions.
Reference
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AEP683

Antitumor effects of growth hormone-releasing hormone (GHRH) antagonists in ACTH- and GH-secreting pituitary neuroendocrine tumor cell lines

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Pituitary neuroendocrine tumors (PitNETs) are mostly benign lesions originating from the anterior pituitary and represent 10–15% of all the intracranial neoplasms. PitNETscan be classified in non-secretory, clinically non-functioning pituitary adenomas (NFPAs), and secretory, comprising prolactin (PRL), growth hormone (GH) and adrenocoticotropic hormone (ACTH) PitNETs. Surgical resectionis the first line treatment for PitNETs, whereas chemotherapy and radiotherapy are preferred for resistant or metastatic tumors. Growth hormone-releasing hormone (GHRH), apart from promotingpituitary GH secretion, exerts many extrapituitary functions, including stimulation of cell proliferation and survival. GHRH, GHRH receptor (GHRH-R) and splice variant 1 (SV1) of GHRH-R, are expressed in different cancer cell types, where they promote cell proliferation and tumor progression. Conversely, GHRH antagonists inhibit the growth of different tumors *in vitro* and *in vivo*; moreover, it has been demonstrated that first generation GHRH antagonists reduce GH secretion in tumoral rat GH-secreting (GH3) cells. However, to date the role of GHRH antagonists in PitNETs remains largely unknown. Thus, we aimed to clarify the role of last generation GHRH antagonists, MIA-602 and MIA-690, on survival, apoptosis and hormone secretion using murine ACTH-secreting PitNETs cells (AtT-20/D16v-F2)and rat PRL- and GH-secreting PitNET cells, transfected with human GHRH-R(GH3-hGHRHR). Our results show that MIA-602 and MIA-690 dose-dependently reduced cell survival and promoted apoptosis in tumoral ACTH-secreting cells and GH3-hGHRHR; in addition, we observed an increase in expression of the proapoptotic protein BAX and the tumor-suppressor protein P53,paralleled by a reduction of the antiapoptotic protein Bcl-2. MIA-602 and MIA-690 also reduced colony formation and expression of c-Myc oncoprotein, indicating inhibitory activity on migration and proliferation. Furthermore, the combination of MIA-602 or MIA-690 with Temozolomide (TMZ), the main chemotherapy agent for PitNETs, produced a synergistic effect on inhibition of cell survival in AtT-20 cells. Finally, both antagonists were able to modulate the secretion of ACTH and GH in AtT20/D16v-F2 and GH3-hGHRHR, respectively. Overall, these results indicate that GHRH antagonists display antitumor activities in ACTH and GH cell lines and suggest their potential use for the treatment of PitNETs, alone or in combination with standard therapies.

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AEP684

Evaluation of somatostatin and dopamine receptor expression in non-functioning pituitary adenomas

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Introduction
Non-functioningpituitary adenomas (NFPAs) are of benign nature but a sizeable number of NFPAs show aggressive features. Surgery is not always effective in treating NFPAs and thus other therapeutic options are needed. Previous studies have reported that NFPAs express somastostatin receptors (SSTRs) and dopamine receptors (DRDs).
Aim
To systematically analyze the expression of SSTRs and DRDs in a large cohort of clinically well-characterized patients with NFPAs and analyze their potential association with relevant clinical and molecular aggressive features.
Methods
Retrospective study with 113 patients that underwent transsphenoidal surgery in our center. Relevant clinical variables including invasion, surgical cure, recurrence and histological subtype were obtained to analyze potential associations between these variables and DRD and SSTR expression. Real-time quantitative PCR (qPCR) was used to evaluate SSTT and DRD expression. SSTRs was also by immunohistochemistry (IHQ) in. Histological markers E-cadherin, Ki-67 and p53 were also analyzed by IHQ.
Results
As assessed by qPCR, SSTR3 was the predominant SSTR subtype detected, followed by SSTR2, SSTR5, and SSTR1. A similar expression pattern was observed by IHQ. 84% of NFPAs showed elevated SSTR3 levels and 27% of NFPAs showed elevated SSTR2 expression levels. However, only 11% of NFPAs showed high SSTR5 levels. Regarding DRD expression, DRD2 was the predominant DRD subtype, followed by DRD4, DRD5, and DRD1. Only a minor portion of NFPAs displayed substantial Ki67 and p53 levels. No significant associations between SSTR and DRD expression and tumor size, invasion, cure after surgery, E-cadherin, Ki67 and p53 levels.
Conclusions
No associations between SSTR and DRD expression and clinical and molecular aggressive features were found in NFPAs. A notable number of NFPAs displayed substantial SSTR2 and SSTR5 levels providing a rationale for the potential use of SSTR2 and SSTR5 agonists in these groups of NFPAs.
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AEP685

High prevalence of pituitary deficiency after cranial radiation therapy for skull base meningioma: The importance of an annual screening.

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Purpose
To determine the risk of developing hypopituitarism after cranial irradiation for skull base meningiomas. Cranial irradiation is often chosen as first treatment in skull base meningiomas to avoid risk to proximally-located critical structures. While cranial irradiation has been associated with high risk of inducing hypopituitarism, few studies concern meningiomas.
Methods and materials
Fifty-two adult patients receiving photon-beam therapyfor skull base meningiomas between 1978 and 2014 were included. All five anterior pituitary axes were screenedusing baseline blood measurementsbefore radiotherapy, then each year until March 2019. The pituitary gland (PG) was delineated on CT and the mean dose to it was estimated.
Results
Mean age at diagnosis was 56 years ±14 and 80% were women. Median follow-up was 7 years. Sixty percent of patients developed hypopituitarism (all 5 axes involved) 10 years after the radiotherapy. The frequency of gonadotropic, TSH, ACTH and GH deficiencies as well as hyperprolactinemia10 years after the radiotherapy was 37%, 28%, 18%, 15% and 13% respectively. Twenty-one percent developed deficiencies of two axes only, however noone-axis deficiency was observed. In the multivariate analysis, an estimated dose to the PG ≥ 50 Gy or a meningioma ≥40 mm significantly increased the risk of developing hypopituitarism.
Conclusion
Cranial radiation therapy in the treatment of skull base meningioma is correlated with a high risk of developing hypopituitarism (60% prevalence after 10 years), particularly when associated with tumor size of ≥ 40 mm and an estimated radiation dose to the PG ≥ 50 Gy. The gonadotropic axis was the most frequently affected.
Annual follow-up appears therefore necessary to identify patients requiring treatment for such deficiencies.
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Role of 68ga-dotatoc pet/ct in the management of neuroendocrine tumors

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Introduction
Primary tumours in some patients with metastatic neuroendocrine tumors (NET) cannot be found by conventional imaging as CT, MRI and scintigraphy. ^{68}Ga-DOTATOC PET/CT (^{68}Ga-PET) appears to have superior sensitivity, specifity, and better resolution than ^{99m}TC-octreotide SPECT/TC (SSTR scintigraphy) and can improve decision-making process, however its cost is higher, and its availability is limited.
Aims
Evaluate the role of ^{68}Ga-PET in diagnosis, staging, re-evaluation and change of treatment in a group of NET patients with controversial diagnosis.
Material and methods
In the last 8 months we performed a ^{68}Ga-PET in 19 controversial NET. We collected demographic data, tumor grade, location, NET therapy, 6 months-previous CT and/or MRI and SSTR scintigraphy as well as indication and results of ^{68}Ga-PET.
Results
19 patients were evaluated, Ten males and nine females, mean age of 56±14.2 years. Location of NET: 5 unknown primary tumor (3 metastatic disease and 2 ectopic ACTH secretion), 7 pancreatic NET (6 out of them with metastatic disease), 4 midgut NET, 2 paragangliomas and 1 gastric NET. Grade of NET: G1: 3; G2: 8; G3 1; NEC: 1. Function: 2 producing ACTH (all with unknown primary tumor). Metastasic disease: 5 with hepatic metastasis, 6 with hepatic and extrahepatic disease and 1 with bone and lung dissemination. Indication of ^{68}Ga-PET: 5 for unknown primary NET, 6 for re-staging, 3 for staging after diagnosis, 4 for evaluatingresponse to treatment and 1 for diagnosis. In 2 patients with metastatic unknown NET, ^{68}Ga-PET found primary midgut NET, but none of unknown ectopic ACTH secretion tumors were found. In 11 patients (57.9%), more lesions in ^{68}Ga-PET than in SSTR scintigraphy were detected. In 9 patients (47.4%) ^{68}Ga-PET allowed changes in decision-making process.
Conclusions
^{68}Ga-PET can be useful for diagnosis, re-staging and re-evaluation for recurrence and can lead to changes in management in controversial NET patients.
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Endoscopic transsphenoidal pituitary surgery (ETPS) for pituitary tumors: Outcomes and complications

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Methods
Restrospective descriptive study of patients who underwent ETPS for pituitary adenoma removal performed by the same surgical team in Virgen del Rocio Hospital of Seville from January 2014 to January 2019.
Results
174 patients had a pituitary adenoma (44 GH, 36 ACTH, 94 Non functioning). 54.02% were female. In acromegaly, 39 (88.63%) patients were operated by ETPS as initial approach. 20 (51.28%) patients had cavernous sinus invation. At outcome analysis, 28 (71.19%) achieved biochemical and morphological remission; Cure rate was 100% for microadenomas, 67.66% for macroadenomas, 89.47% for non-invasive adenomas and 55% for invasive adenomas. Additionally, 5 patient with persistant disease after microscopic transsphenoidal surgery (MTS) were operated by ETPS, 3 (60%) were cured. 75 nonfunctioning adenomas were operated by ETPS as initial approach. After surgery, 46 (61.33%) were cured, with similar rates for invasive (59.57%), non-invasive (59.57%) adenomas and tumors larger than 25 mm (54.72%). 47 (62.67%) patients had visual impairment before surgery, 27 (57.44%) patients developed a full recovery after the surgery. 19 patients were operated by ETPS after unsuccessful MTS. Regrowth of pituitary remmant was observed in all reinterventions, 11 (57.89%) presented new campimetric deficits; after the intervention 6 (31.58%) reached cure criteria, with a cure rate for invasive adenomas of 33.33%; 10 (90.9%) presented full o partial recovery of visual impairment. 27 ACTH secreting adenomas were operated by ETPS by first time. After the surgery, 22 (81.48%) patients were cured. 9 patients were reoperated after an unsuccessful MPS, 6 (33.33%) were macroadenomas. 6 (66.67%) patients with a second operation were cured. Regarding complications, 2 patient had LCR fistula, 4 suspiction meningitis and 2 epistaxis.
Conclusions
The cure rates observed in our series were higher tan in the most MPS published series. Reintervention is an adequate treatment approach in cases of recurrence and resistant Cushing disease and Acromegaly.

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Do cardiovascular risk factors predispose to pituitary apoplexy?

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Introduction
Pituitary apoplexy (PA) is a rare incident defined by the occurrence of necrosis and/or haemorrhage of the pituitary gland. The low incidence of PA makes it difficult to bring out from the studies its precipitating factors and especially its relationship with cardiovascular risk factors (CVR). The objectives of this studies were to characterize a number of patients with PA and to establish the link between PA and their CVRs.
Methods
It is a retrospective study including a group of patients in the Endocrinology department of Hedi Chaker Hospital in Sfax over an 18-year period (2000 – 2017). The data collected was analysed by the SPSS version 20 software.
Results
This study included 44 patients (20 women versus 24 men) with a mean age of 50.04±12.58 years. Fourteen patients (31.8%) had a pituitary adenoma known before the onset of apoplexy, secreting in 9 cases. Precipitating factor have been found in 14 cases (31.8%). A high blood pressure was found in two cases. CVR were dominated by the presence of overweight in 27 patients (61.4%) and android obesity in 17 patients (38.6%), followed by smoking in 15 patients (34%) and type 2 diabetes in 11 patients (25%). Four patients had treated dyslipidaemia at diagnosis (9.1%): two patients had mixed dyslipidemia treated with atorvastatin andtwo patients had isolated hypertriglyceridemia treated with fibrates. Two patients had a cardiac history: unstable angina in one case andcoronary disease in the second. We analysed these features and we found no correlation between these factors and the occurrence of PA.
Conclusion
We conclude through these data that having weather a metabolic syndrome or a documented cardiovascular disease do not precipitate the occurrence of PA in patient with pituitary adenoma. We explain these results with the low number of this cohort and of the pathology itself.

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AEP689

Trabecular bone score as a useful tool for assessment of fracture risk in acromegaly

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Acromegaly is a rare disease, caused by an excessive secretion of growth hormone (GH), and consequently the insulin like growth factor 1 (IGF-1). Patients with acromegaly have an increased risk of fractures, which might be correlated with insufficient quality of bone. It is known that use of FRAX in acromegaly is not validated, however we do not have other useful tools to assess real risk for fractures. The new valuable tool in the assessment of bone structure is the trabecular bone score (TBS) measurement, which provides some information on bone microarchitecture from a routine DXA. The high TBS score reflects better bone structure, whereas a low TBS score indicates impaired bone structure associated with higher fracture risk.
Purpose
The aim of this study was to assess the usefulness of TBS in prediction of fractures in patients with acromegaly.
Materials and methods
We studied 63 patients with acromegaly and 42 healthy controls (CG). Acromegaly patients were divided into three subgroups on the basis of disease activity (AA – active acromegaly, CTA – controlled treatment acromegaly (during somatostatin analogues therapy) and CA – cured acromegaly). In all patients blood samples were obtained to assess the hormonal and metabolic status. The bone mineral density (BMD) of the lumbar spine (LS) (L1-L4), femoral neck (FN) was measured using the dual-energy X-ray absorptiometry (DXA) method by densitometer. All TBS values were analyzed using the TBS iNsight software, (Med-Imaps, Pessac, France) using spine DXA files from the database.
Results
Lumbar spine TBS was significantly lower in the whole acromegaly group (AA+CTA+CA) vs CG (1.22±0.13 vs 1.29±0.10, $P=0.019$). In contrast, BMD at all sites did not differ between these groups. Additionally, TBS was significantly higher in CG compared to CTA (1.29±0.10 vs 1.18±0.12, $P=0.00$) as well as to CTA+CA (1.29±0.10 vs 1.21±0.14, $P=0.00$). Similarly, BMD also did not differ among these groups. The risk of major fractures and hip fractures was significantly higher in the whole acromegaly group as well as in CTA+CA and in CTA compared to CG ($P=0.00$ for all).
Conclusions
The present results confirmed the higher risk of fractures in acromegaly patients despite of BMD results. Low TBS score reflects worse bone structure in acromegaly. TBS may be a useful tool for predicting risk of fractures in acromegaly patients.

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AEP690

Metabolic abnormalities in patients with childhood onset of hypopituitarism – single center,long term observation

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Background
Hypopituitarism is a condition caused by deficiency in one or multiple pituitary hormones. The disease is associated with various metabolic disorders and decreased quality of life that are particularly marked in patients with childhood onset of the disorder. There are manyfactors influencing the metabolic status of patients such as different treatment modalities (surgery, radiotherapy, chemotherapy) and current supplementation (e.g. steroid or testosterone/estradiol substitution)which should be taken into consideration. This specific group of patients requires an extensive care because of increased risk of metabolic abnormalities.
Aim
To present the metabolic characteristic of patients with childhood onset of hypopituitarism on the basis of long term observation in the pediatric/adult endocrinology departments of our university.
Methods
We analyzed retrospectively current complete data of 35/75 patients with childhood onset of pituitary dysfunctions (13 W/22 M). 28/75 patients with PROP-1 mutation were excluded from this study due to the separate analysis. Etiologically, congenital malformations were found in 13/35 of patients; 10/31 were treated for craniopharyngioma, 3/35 for histiocytosis, 2/35 for germinoma. The mean age of diagnosis was 9.18 years (s.d. 4.8).
Results
29/35 of patients presented with somatotropic axis deficiency. Deficits in gonadal, thyroid and adrenal hormones were detected in 26/35, 25/35 and 18/35 of patients, respectively. Body weight abnormalities were found in 24/35 of patients (obesity in 9/35 of patients, overweight in 10/35 of cases and underweight in 5/35 of them). Extreme values were observed in patients operated for craniopharyngioma (cachectic patient with BMI 16,9 and obese one with BMI 46,5). Systolic and diastolic blood pressure were higher in 6/35 and 8/35 cases, respectively. 18/35 of patients were diagnosed with various lipid disturbances (among them 15/25 of patients with central hypothyroidism and 15/29 with somatotropic pituitary dysfunction). Kidney function was preserved in all patients. 8/35 of patients had at least one liver enzyme elevated. Vitamin D deficit was found in 12/35 of cases. Oral glucose tolerance test (performed in 26/35 of patients) revealed diabetes in 1 case, impaired glucose tolerance in 3 patients (all of them had secondary hypoadrenalism and were treated with hydrocortisone) and confirmed insulin resistance (IR) in 14/26. The highest incidence of IR were observed in patients with history of craniopharyngioma (6/7) and histiocytosis (2/2).
Conclusions
Majority of patients with childhood onset of hypopituitarism characterizes with at least one metabolic dysfunction. Proper management of hormonal abnormalities and early administration of treatment might preserve these patients from serious consequences.

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AEP691

Early basal growth hormone level and nadir growth hormone level in oral glucose tolerance test as predictors for surgical cure in acromegaly

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Introduction
Growth hormone (GH) level is a direct marker of active residual adenoma tissue after acromegaly surgery. However, the value of early postoperative GH for prediction of surgical cure in acromegaly has not been established and therefore is not used in everyday clinical practice.
Aim
The aim of our work was to study the 24-hour basal postoperative GH level and the nadir of GH level after the oral glucose tolerance test (OGTT) two weeks after surgery as predictors of surgical cure in acromegaly.
Materials and methods
A prospective cohort study included patients with newly diagnosed acromegaly. All patients underwent transsphenoidal surgery (TSS) performed by one neurosurgeon. The basal GH level 24 hours after surgery and the nadir GH in OGTT carried out two-weeks postoperatively were measured in all cases. The results of TSS were estimated twelve months after operation. The biochemical remission of acromegaly was defined as nadir GH level in on an OGTT < 0.4 µg/l along with age and gender normalized values of insulin-like growth factor 1 (IGF-1).
Results
Thirty-nine patients (32 women and 7 men) with mean age 53.0 ± 7.9 years (35–63 years) were enrolled into the study. 31 patients harbored macroadenomas (79.4%). Remission rate was 46.1% (18/39) on follow-up after 12 months (in microadenomas it was 75% (6/8), in macroadenomas – 38.7% (12/31)). Preoperative basal GH and IGF-1 levels did not differ in remission and persistence groups. Basal 24-hour postop GH level decreased in all patients when compared with baseline and was significantly lower among patients in remission group: 1.8 ± 0.9 vs 5.3 ± 2.8 µg/l, $P = 0.0002$. The GH level <1.30 µg/l showed the highest prognostic value for acromegaly remission with sensitivity of 93.7% (95% CI, 81.1–98.3) and specificity of 83.5% (95% CI, 60.1–93.8). The nadir GH level <1.0 µg/l in two-week postop OGTT had a sensitivity of 85.7% (95% CI, 60.1–97.5) and specificity of 80.0% (95% CI, 54.8–92.9) in prediction of acromegaly remission 12 monthsafter surgery.
Conclusion
Early postoperative GH level can predict the outcome of surgical treatment in acromegaly. Our data suggests that the basal 24-hours postoperative GH < 1.3 µg/is a stronger predictor of acromegaly remission after TSS than the nadir GH < 1.0 µg/l in two-week postop. These findings require further research.

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AEP692

Quantitative bone assessment by radiofrequency echographic multi-spectrometry (REMS) in patients with acromegaly – a preliminary study

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Introduction
Acromegaly is a rare diseaseresulting most commonly from pituitary adenoma. A chronic increase of growth hormone (GH) and insulin-like factor 1 (IGF-1) leads to many systemic complications including osteoporosis and fractures. Radiofrequency echographic multi-spectrometry (REMS) is a new non-ionizing technique to diagnose osteoporosis.
Purpose
The objective of the study was to evaluate bone mineral density (BMD) by REMS in patients with well-controlled and cured acromegaly. The associations between BMD measured by REMS and GH, IGF-1 concentrations and BMD measured by dual energy X-ray absorptiometry (DXA) were investigated in acromegaly patients.
Material and methods
The study group comprised 33 patients with acromegaly and 24 controls (CG). Based on clinical picture and hormonal evaluation (GH and IGF-1 concentrations) the acromegaly group was divided into two subgroups: well-controlled acromegaly (WCA) – (normal IGF-1 during somatostatin analogues therapy) and cured acromegaly (CA) – (normal IGF-1, patients after successful surgery). Blood samples were obtained from patients with acromegaly to measure concentrations of GH and IGF-1. REMS was performed in all participants, whereas DXA in the acromegaly group only.
Results
There were no significant differences in T-score, Z-score and BMD measured by REMS at lumbar spine (LS) and femoral neck (FN) among the subgroups of patients with acromegaly and controls (WCA, CA and CG). Similarly, we did not observe significant differences in T-score, Z- score and BMD measured by DXA at LS and FN between WCA and CA groups. IGF-1 concentration correlated positively with T-score, Z-score and BMD measured by REMS and DXA at LS and FN in the WCA + CA and WCA groups ($P < 0.05$). No significant correlations were observed between GH levels and T-score, Z-score and BMD measured by REMS and DXA. Positive correlations between BMD LS assessed by DXA and BMD LS evaluated by REMS were found in WCA + CA and CA groups. There were no significant correlations between BMD FN measured by REMS and DXA.
Conclusion
The present study shows potential utility of REMS assessment of trabecular bone deterioration in acromegaly, as shown by results obtained in lumbar spine. There are no differences in BMD measured by REMS in patients with well-controlled and cured acromegaly. The association between IGF-1 concentration and BMD may suggest an anabolic action of IGF-1 in well-controlled acromegaly.

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AEP693

Analysis of the value of bilateral inferior petrosal sinus sampling in the diagnosis and treatment of Cushing's disease in patients with a negative or inconclusive result of magnetic resonance imaging

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Diagnosis and treatment of Cushing's disease is one of the greatest challenges of modern endocrinology. This is related to the fact that pituitary corticotropinomas are small tumours that are difficult to visualize in magnetic resonance imaging (MR). In about 40% of patients with Cushing's disease, MR scans of the pituitary gland do not reveal any changes. The method that allows to localize the source of adrenocorticotropin (ACTH) secretion is bilateral inferior petrosal sinus sampling (BIPSS), which has so far been performed rarely in our country. The treatment of choice of this disease is transphenoidal resection of corticotropinoma allowing remission of hypercortisolemia in 64–98% of operated patients. The results of surgical treatment depend to a large extent on locating the source responsible for excessive ACTH secretion. The aim of this study was the assessment of usefulness of bilateral inferior petrosal sinus sampling in diagnosis and treatment of Cushing's disease in 74 patients with negative or inconclusive MR imaging of pituitary adenoma. All patients had BIPSS performed and ACTH values were used to assess the ratio of the concentration in central vs peripheral blood and between right and left inferior petrosal sinus before and after administration of CRH. Confirmation of the pituitary secretion of ACTH-dependent hypercortisolemia was obtained in 68 patients, in 6 patients the result indicated ectopic ACTH secretion. All patients with pituitary ACTH secretion underwent a transsphenoidal operation, which in three cases (4.4%) did not lead to a cure. A statistically significant correlation was also shown between BIPSS result and localization of adenoma confirmed intraoperatively. The results of bilateral inferior petrosal sinus sampling in patients with Cushing's disease and negative or inconclusive result of pituitary imaging presented in the study allow for differentiation of the pituitary and non- pituitary source of ACTH secretion and are highly helpful in localization of corticotropinomas, as well as affect the effectiveness of surgical treatment. It has been demonstrated that the greatest diagnostic significance during bilateral inferior petrosal sinus sampling have results obtained in the 3rd minute after CRH administration and that BIPSS is a safe and well-tolerated procedure. In the group of ACTH-secreting pituitary adenomas examined, the diameter of the tumor was the only significant factor influencing the effectiveness of surgical treatment.

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AEP694

Micromegaly or acromegaly? A retrospective longitudinal study on clinical aspects and comorbidities in a large cohort of patients referred to a single tertiary center

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Introduction
The diagnosis of acromegaly is confirmed in the presence of high IGF-1 levels and inadequate suppression of growth hormone (GH) after glucose load. According to guidelines, a GH nadir (GHn)>0.4 ng/ml is considered diagnostic with ultrasensitive assays. However, some acromegalic patients with lower GHn, also called 'micromegalic', are reported, but a systematic collection of their clinical features is unavailable.
Aim of the study
The main aim was to characterize a group of patients with high IGF1-levels but GHn < 0.4 ng/ml, focusing on acromegalic clinical features and comorbidities. The second one was to evaluate the clinical and hormonal progression over time.
Materials and methods
We performed a longitudinal retrospective study, including 49 patients referred to the Endocrinology Unit of the Ospedale Maggiore Policlinico, from 2009 to 2019, who presented high IGF-1 levels and GHn <0.4 ng/ml. GH was measured with an ultrasensitive assay. Data on typical acromegalic clinical features, comorbidities, pituitary imaging, IGF-1, GHn and GH random were collected, both at the time of the first finding of high IGF1 (diagnosis) and at the last follow up (FU).
Results
At diagnosis, mean age was 53.9 ± 16 S.D. years and 30/49 were females. Diagnostic evaluations started because of acromegalic facies in 45%, pituitary disease in 43% and various endocrinopathies in other ones. Patients with acromegalic facies showed a high prevalence of comorbidities, overlapping with those of classic acromegaly: glucose metabolism alterations in 82 vs 44% in patients with facies and without facies respectively, hypertension in 59 vs 28%, goiter in 50 vs 28%, carpal tunnel in 41 vs 4%, neoplasms in 41 vs 12%, cardiopathy in 36 vs 20%, colonic polyposis in 23 vs 16% (note that only 14 colonoscopies were performed). The ANOVA analysis showed that patients with a higher number of comorbidities had higher GHn levels (P 0.036) and GHn > 0.1 ng/ml was strongly associated with the presence of specific comorbidities (carpal tunnel OR 5.4, goiter OR 4.8 etc.). Pituitary imaging was available in 41/49 showing an adenoma in 16/41 (4 macro, 16 microadenomas) with other 4 new microadenomas at the last FU. Mean FU was 4.4 ± 3.2 years and we observed an increase of some comorbidities (hypertension + 20%, neoplasms + 20% and goiter + 16%), while IGF1 and GH levels did not significantly change.
Conclusions
Patients with acromegalic features, high IGF1 levels but a GH nadi r < 0.4 ng/ml, also called 'micromegalic', seem to clinically overlap with classic acromegaly. In our group, acromegalic facies and GHn > 0.1 ng/ml are strongly associated with comorbidities that, unlike IGF1 and GH, seem to worsen over time.

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Markers of recurrence in cushing's disease: The role of post-operative serum cortisol and desmopressin test

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Introduction
Transsphenoidal surgery (TSS) is the first-choice treatment in Cushing's disease (CD). When performed by experienced neurosurgeon, post-operative remission can be achieved in 70–80% of cases; however, recurrences during follow-up are quite frequent, involving around 20–30% of patients initially in remission. Early detection of relapses is crucial to avoid cortisol-related comorbidities. The aim of the study was to find reliable predictors of recurrence after neurosurgery in patients with CD.
Materials and methods
Forty CD patients (32 F/8 M, median age at diagnosis 39 years, range 13–67) in remission after TSS and with postoperative follow-up of at least 24 months (median 121.5, range 27–212 months) were included in the study. Remission was defined in the presence of at least two of the following criteria: i) post-surgical hyposurrenalism; ii) normal urinary free cortisol (UFC) and late-night salivary cortisol (LNSC) for at least 12 months; iii) serum cortisol < 50 nmol/l after 1 mg dexamethasone suppression test. All patients were submitted to at least one desmopressin (DDAVP) test during follow-up (6–12 months after surgery) and in 37/40 cases even in the diagnostic phase.
Results
Nine patients (22.5%, 8 F/1 M) experienced disease recurrence after a mean time of 32.2 months (range 18–62). Patients with macroadenomas were more prone to recur postoperatively P = 0.003). Early post-operative serum cortisol was lower in patients in prolonged remission compared to that of relapsed patients (55.5, IQR 33.3–54 nmol/l vs 191.5, IQR 57.5–417.5 nmol/l, P = 0.025), even though there was some degree of overlap between groups. A threshold of 76 nmol/l for serum cortisol was able to identify patient

at high risk of relapse with sensitivity (SE) and specificity (SP) of 75%. Patients with recurrence displayed a greater ACTH and cortisol response ($P=0.0001$) to DDAVP test compared to those in prolonged remission. An absolute increase in ACTH>7.6 ng/l was identified through the ROC curve analysis (AUC=0.8796; 95% CI :75–100) as the best predictor of recurrence, with SE of 88.9% and SP of 83.3%. After TSS, no differences in UFC and LNSC values were observed between groups.
Conclusions
The presence of corticotroph macroadenoma is a risk factor for CD relapse. DDAVP test is more accurate than the evaluation of serum cortisol in the immediate post-surgical period in predicting late recurrence. The re-appearance of a positive response to this test is an early marker of future relapse, that precedes the increase in LNSC and UFC by several months thus patients displaying such alteration should be closely monitored.

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Long-term response to cabergoline treatment in men with macroprolactinoma is independent of tumor size

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Objective
To study the outcomeof menwith macroprolactinoma followingcabergoline treatment based on tumor size.
Design
A retrospective cohort study using a single tertiary referral center registry.
Methods
The study included 96 men with macroprolctinoma, aged 16–84 years (mean 47.3 years) treated from 1993 to 2019,for a mean follow-up of 7.5 years. The cohort was subdivided into 3 groups according to baseline adenoma diameter: group A, adenomas of 10–19 mm ($n=36$), group B,20–39 mm ($n=43$), and group C,giant prolactinomas ≥40 mm ($n=17$). Cabergoline was started at a weekly dose of 0.5 mg and progressively increased as necessary (weekly cabergoline dose, 0.5–10 mg). Nineteen men required pituitary surgery, 3 (8%), 10 (23%), and 6 (35%) in group A, B and C, respectively.
Results
Mean prolactinoma maximal diameter at presentation was 15.0, 28.1 and 49.8 mm in group A, B and C, respectively, decreasing following treatment to 7.6, 13.6 and 16.6 mm ($P<0.01$). Mean baseline prolactin levels were 685, 2,134 and 24,316 ng/ml ($P<0.01$) in group A, B and C,decreasing following treatment to 15, 68 and 31 ng/ml ($P=0.48$). Prolactin suppression to <3 ×ULN was achieved in 34 (94%; mean weekly cabergoline dose, 1.2 mg), 35 (81%; cabergoline dose, 2.0 mg) and 14 (82%; cabergoline dose, 2.8 mg) men ($P=0.21$) in the different groups. Treatment duration until complete prolactin normalization was 10.8, 17.9 and 21.9 months, occurring in 33 (92%), 31 (72%) and 14 (82%) men in group A, B and C, respectively. Visual defect was depicted in 4 (11%), 14 (33%) and 9 (56%) patients ($P=0.03$) in group A, B and C, respectively. Improvement was achieved in 4/4, 13/14 and 9/9 men. Residual visual field impairment at the end of follow-up was noticed in 0 (0%), 7 (16%), and 6 (40%) patients ($P=0.01$)in group A, B and C, respectively. Low baseline testosterone was discovered in 26 (72%), 40 (93%) and 17 (100%) patients ($P<0.01$) in group A, B and C. Hypogonadism following treatment persisted in 2 (6%), 5 (11%) and 2 (12%) men, respectively ($P=0.61$). Sexual dysfunction at presentation was reported by 23 (68%), 33 (79%) and 14 (82%) patients in group A, B and C, respectively, but improved in 21/23 (91%), 25/29 (86%) and 10/13 (77%) patients in the different groups.
Conclusion
Cabergoline is very effective in most men with macroprolactinoma, regardless of initial tumor size.

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Abstract withdrawn

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Inferior petrosal sinus sampling – 16 years of experience from a single tertiary center in Israel

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Introduction
IPSS (Inferior petrosal sinus sampling) is a reliable test for differentiating Cushing's disease from ectopic ACTH secretion. In the past 30 years, Hadassah Hebrew University Hospital has been the sole national referral center for IPSS in Israel, carrying out the test for all patients country-wide.
Methods
In this retrospective study we reviewed the records of all patients who underwent IPSS in our institution, for whom electronic data were available. Medical records were reviewed, and additional information was collected from the referring endocrinologists.
Results
Between 2003 and 2019 IPSS was performed in 63 patients. Male/female ratio was 19/44 and the average ± s.d. age was 45.1±14.9. Indications for referral included: absence of a visible pituitary adenoma on MRI (43patients, 68.3%); inconclusive biochemical testing (16 patients, 25.4%); and persistent hypercortisolemia following prior pituitary surgery (12 patients, 19.0%). Over one indication per patient may have been listed. IPSS results compatible with pituitary ACTH secretion were found in 52/63 patients (82.5%), of whom 48/52 (92.3%) underwent subsequent pituitary surgery. Biochemical cure was reported for 31/52 patients (59.6%) and 6/52 (11.5%) had residual or recurrent disease, although pathological results indicated pituitary adenoma. Thus, in 37/52 (71.2%) patients with IPSS results compatible with pituitary ACTH secretion, Cushing's disease was confirmed. The final outcome was unknown in 15/52 (28.8%) patients, of whom 4 did not undergo surgery and in 11 hypercortisolemia did not resolve following surgery and confirmatory pathology results were unavailable. IPSS test results were consistent with ectopic ACTH secretion in 11/63 patients (17.5%). A documented ACTH secreting ectopic tumor was discovered in 4 patients (1 medullary thyroid carcinoma and 3 carcinoid), 3 were found to harbor an adrenal adenoma and in 2 the source of ACTH hypersecretion was not found. Pituitary surgery was performed in two patients in spite of IPSS results indicating an ectopic source of ACTH, and their hypercortisolemia had subsequently resolved. Overall, IPSS correctly established the diagnosis in 44 (69.8%) patients – accurately revealing a pituitary source in 37 patients and a non-pituitary source in 7 patients. A false negative result was noted in 2 patients (3.2%). The high rate of inconclusive outcomes (17/63, 27.0%) precludes reliable estimation of sensitivity and specificity of the test. No major complications of the IPSS procedure were documented.
Conclusions
In this select population of diagnostically challenging patients with Cushing syndrome, IPSS was safe and feasible, and led to definitive diagnosis in 69.8% of the patients.

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Determinants of epicardial fat in patients with acromegaly

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Background
Epicardial adipose tissue (EAT), the visceral fat of de myocardium, has been positively related to insulin resistance (IR), cardiovascular risk and the left ventricular myocardial mass. Whether EAT thickness in acromegaly is mediated by GH/IGF-1, IR or other factors remains to be elucidated.
Objective
The aims of this study were: 1) To investigate whether EAT in patients with ACRO is linked to IR and pro-inflammatory and anti-inflammatory related cytokines, 2) To examine whether EAT is related to circulating GH/IGF-1 and its metabolic signature: low serum levels of branched amino acid (BCAAs). 3) To assess whether EAT is related to myocardial hypertrophy.
Methods
Thirty patients with acromegaly were included in the study. EAT andventricular myocardial masswere assessed by echocardiography. Circulating levels of pro-inflammatory and anti-inflammatory cytokines, glucose and insulin were measured using commercial kits. Serum BCAAs were assessed by 1-H-MR.
Results
We analysed 30 patients: 5 were active despite medical treatment, 14 controlled and 11 in remission. EAT was positively associated with HOMA-IR (rho: 0.40, p:0.03)). Conversely adiponectin, was negatively correlated (rho: –0.43 p: 0.02). We did not find any relationship between EAT and GH/, IGF-1 or BCAAs. In addition, EAT was unrelated to myocardial mass.
Conclusion
EAT positively correlated with HOMA-IR and negatively with adiponectin. This relationship seems not to be mediated by GH/IGF-1 or BCAAs. Our results suggest that other factors unrelated to GH/IGF-1 but directly related to IR are the main responsible of the excess of EAT observed in patients with acromegaly.

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Disconnection hyperprolactinaemia and its correlation with tumour size: A study of 210 patients with histologically proven non-functioning pituitary macroadenomas

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Background
Serum prolactin levels at presentation can be useful in distinguishing between non-functioning pituitary macroadenomas and prolactinomas in order to guide appropriate therapy. Although thresholds have been suggested to distinguish between the two tumour-types, there remains some debate regarding discriminatory levels.
Objective
To assess the baseline serum prolactin levels in a series of patients with histologically-proven non-functioning pituitary tumours and to correlate prolactin levels with size of tumour, which may reflect degree of stalk compression.
Methods
Patients presenting to the University Hospital of Wales, Cardiff, with non-functioning pituitary adenomas (histologically proven) between 2011–2019 were studied by examining biochemical, histological and radiological data.
Results
A total number of 210 patients with histologically-proven non-functioning pitutiary macroadenomas were identified (130 male, 80 female). The median age at surgery was 57 yrs (range 24–86 yrs). Median prolactin inthe total group was 408 mU/l (range 3–3390), males 321 mU/l (range 35–1581), females 656 mU/l (range 3–3390). 96/210 (45.7%) patients had a high prolactin. 24/96 (25%) of these patients were on medications that could cause a high prolactin. Median prolactin for patients on medications was 792 mU/l (range 443–3390). Median male prolactin on medications was 766 mU/l (range 443–1450) and in females 792 mU/l (range 618–1880). In the total group, 88.1% had serum prolactin <1000 mU/l and 99.0% <2000 mU/l. Of the 2 patients with prolactin >2000 mU/l, one was taking an oestrogen preparation for initial presumed polycyctic ovary syndrome. There was a negative correlation between tumour size and prolactin levels with Pearson's correlation of –0.09 ($P=0.24$). Those with tumour size <10 cm^3 had mean prolactin 561 mU/l compared to 486 mU/l in those with tumours >10 cm^3 ($P=0.3$).
Conclusions
Our large data series supports previous evidence that serum prolactin is rarely >2000 mU/l in non-functioning pituitary adenomas. In these cases a trial of dopamine agonist therapy is warranted to see if there is any reduction in tumour size. Although a negative correlation between tumour size and serum prolactin was seen, this was not found to be statistically significant.

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Role of 1 mg ACTH Stimulation Test to predict adrenocortical reserve and need of glucocorticoid therapy in non-functioning pituitary adenomas undergoing surgery

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Background
Peri-operative glucocorticoids are routinely administered to patients undergoing trans-sphenoidal surgery for non-functional pituitary adenomas (NFPA) irrespective of the integrity of hypothalamic-pituitary-adrenal (HPA) axis.
Aim
To evaluate HPA axis before and three months after endoscopic trans-sphenoidal adenomectomy (E-TSA) in patients with clinically NFPA utilizing 1 mg ACTH stimulation test and determine the need for glucocorticoid administration.
Design
Open prospective study.
Setting
Tertiary care referral hospital.
Patients
From July 1st, 2017 to December 31st, 2018, 63 consecutive patients (48 ± 12.5 years, M:F = 2.3:1) with intra/suprasellar non-functioning pituitary adenoma requiring surgical excision were enrolled in this study.
Interventions
Glucocorticoids were administered to patients with demonstrable hypocortisolism. Perioperative glucocorticoids were administered to patients with peak cortisol <16 µg/dl during 1 mg ACTH test preoperatively. Postoperatively, glucocorticoids were given to patients with 0800 cortisol <8 mg/dl on the third postoperative day. At three months follow up, glucocorticoids were given to patients with peak cortisol <16 µg/dl on LDACTH test. Main outcome measurements: Stimulated cortisol using low dose (1 mg) ACTH test (LDACTH) was determined preoperatively. After E-TSA, 0800 cortisol was determined on the third post-operative day and LDACTH test was repeated at three months after surgery.
Results
Hypocortisolism was present in 43 patients (68.2%) pre-operatively and persisted in 33 patients (52.4%) on the third post-operative day. Thirty-three patients (52.4%) had hypocortisolism at three months after surgery. Fourteen patients (22.2%) didn't require glucocorticoids during the entire study period and thirty patients (47.6%) didn't require glucocorticoids after three months. None of the patients developed adrenal crisis during the study. There was a significant correlation between postoperative day third 0800 cortisol ≥ 8 mg/dl and stimulated cortisol (LDACTH) ≥ 16 mg/dl at three months ($r=0.62$, $P<0.0001$). Postoperative day third 0800 cortisol <8 mg/dl had 75% sensitivity and 58.1% specificity in predicting adrenal insufficiency at three months after surgery (AUC 0.66, $P=0.026$).
Conclusions
HPA function is preserved in significant proportion NFPA patients undergoing E-TSA. Perioperative glucocorticoids should be given only in patients with demonstrable preoperative hypocortisolism on 1 mg ACTH test. Postoperative day third 0800 cortisol <8 mg/dl is a reasonable predictor of adrenal insufficiency at three months after surgery.

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Gigantism associated with hyperprolactinemia due to a pituitary macroadenoma in an adolescent girl

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Aim
To describe the clinical course of an adolescent girl with gigantism.
Background and methods
In young persons with open epiphyses, overproduction of GH results in gigantism, with consequent longitudinal growth acceleration[1]. Pituitary gigantism is extremely rare, and its cause in the majority of patients is a pituitary adenoma[1]. Here, we present a 12, 5 years-old girl investigated for tall stature [183.5 cm (+4.24 SDS)].
Results
In the case reported here, the girl exhibited significant growth acceleration since she was 7 years-old, with coarsening of her facial features, and scoliosis of her thoracic spine. Her initial workup revealed a high insulin-like growth factor 1 (IGF-1), GH, and prolactin level, with no suppression of GH at the oral glucose tolerance test (OGTT); ACTH and cortisol values as well as thyroid function were within normal ranges. Magnetic resonance imaging (MRI) of the pituitary revealed a homogenous and diffusely enlarged pituitary gland, attributed to a pituitary macroadenoma (7.7×16 mm), which extended outside the pituitary gland. Whole exome sequencing analysis did not show any pathological findings. Thyroid ultrasound revealed cystic and solid nodules, with benign FNA. Firstly, she was treated with octreotide and cabergoline, followed by transsphenoidal surgical removal of the tumor. Postoperative levels of IGF-1 and prolactin decreased significantly; however GH levels at the OGTT test were partially suppressed, consistent with residual disease. Therefore, she underwent adjunctive radiation therapy. At 3-year follow-up, pituitary MRI findings represent an empty sella without significant functioning pituitary tissue, with remaining pituitary tumor mainly at the lateral sides of the sella. Her OGTT shows sufficient suppression of the GH level and her IGF-1 is in the lower side of the normal limit for her age, with stable clinical remission. At present, she is under octreotide treatment with no complaints, while cabergoline was stopped by the time prolactin levels were decreased.
Conclusion
This case demonstrated the difficulty of treating gigantism due to a GH/prolactin secreting pitutitary macroadenoma. At the same time, GH oversecretion is related to nodular thyroid disease, which requires careful evaluation with thyroid ultrasound. Genetic basis of the disease remains unclear in our patient.
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AEP703

Cabergoline resistance in a patient with prolactinoma with debut before puberty

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Prolactinomas are the most common hormone-active pituitary tumors, most common in young women, whose main reason for going to the doctor is menstrual irregularity. At the onset of the disease before puberty in children, there is a delay in sexual development, in girls primary amenorrhea.
A 27-year old woman has been observed since 15 years, when hyperprolactinemia was first detected, level of PRL was 10 900 IU/l, and according to MRI pituitary endosellar microadenoma. Cabergoline therapy was prescribed, which the patient received irregularly. The dose of cabergoline is gradually increased to 3.5 mg per week. However, no decrease in prolactin levels was observed. Adenoma growth was noted. After 7 years of observation, an increase in the size of adenomas with supra-parasellar growth (16×18×26 mm), prolactin levels ranged from 11 230 –16 800 IU/l. In connection with the patient's refusal from surgery, the dose of cabergoline was increased to 4.5 mg per week. However, against this background, no positive dynamics were observed. During the entire observation period, the patient has primary amenorrhea, decreased libido, and obesity (BMI 35). On examination: the mammary glands are not sufficiently developed. At the age of 32, the patient began to notice headaches. When examining PRL was 16800 mU/l, the negative dynamics of the size of the adenoma: dimensions 21×22×18 mm with parainfrasurpasellar growth, the distance to the chiasm 2.5 mm. The patient is again offered an operation, to which she agreed. The patient underwent transnasal transphenoid adenomectomy. The histological examination and immunohistochemistry of surgical sample confirmed PRL-secreting pituitary adenoma, Ki-67–7.4%, positive p53. In hormonal blood tests in the postoperative period, the prolactin level is 498–742 IU/l. There were no signs of diabetes insipidus, adrenal insufficiency, or secondary hypothyroidism. 2 months after surgery, menstruation first came. In terms of monitoring and, if necessary, the appointment of hormone replacement therapy with sex hormones This clinical case demonstrates the delay in sexual development in a girl of 15 years with hyperprolactinemia, as well as the success of transnasal adenomectomy with resistance to cabergoline.

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AEP704

A rare etiology of hyperprolactinemia: Factitious hypoglycemia

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Introduction
While prolactin is most well known for its role in lactation and suppression of reproduction, its physiological functions are quite diverse. There are many etiologies of hyperprolactinemia, including physiologic as well as pathologic causes. Factitious hypoglycemia a rare case of induced hyperprolactinemia
Case report
We report a case of 17-years-old girl presented to with sever hypoglycemia mesured at 30 mg/dl. The patient had no significant medical personal history, and she had a younger sister with type 1 diabetes mellitus. Physical examination of the patient showed: weight of 44 kg, BMI = 20 kg/m^2 and bilateral induced galactorrhea with no other abnormalities. Laboratory analysis revealed normal renal and hepatic function and confirmed the exogenous injection of insulin with hyperinsulinism at 191uUI/ml and low C-peptid level 0.71 ng/ml concomitant to hypoglycemia at 37 mg/dl. Endocrine studies were notable for high levels of prolactin 3063 mUI/ml (102–496 mUI/ml), normal adrenal gland function (cortisol = 512 nmol/l after Synacthen test) and normal thyroid hormones level (TSH = 0.67 uUI/ml and FT4 = 17.95 pmol/l). Magnetic resonance imaging of the pituitary gland was done and showed no abnormalities. The patient was referred to psychiatric evaluation and management. On follow up she had no recurrent episodes of hypoglycemia, she had no more galactorrehea and prolactin level returned to normal in 3 weeks (prolactin = 370 mUI/ml).
Conclusion
It is known that are many physiologic and pathologic causes of hyperprolactinemia. Stress is an important physiologic cause of hyperprolactinemia, and its clinical significance is still being explored. We report a rare case of factitious hypoglycemia as cause of stress-induced hyperprolactinemia.

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AEP705

Pituitary gland metastasis of endometrial cancer: A case report

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Introduction
Tumour metastasis to pituitary gland is very rare and constitutes only 1% of all pituitary lesions. Breast and lung cancer are the most common neoplasms reported to metastasize to pituitary gland. Most of the pituitary metastasis are asymptomatic, and thus can be easily overlooked in imaging studies.

Polyuria and polydipsia due to diabetes insipidus are the most common sypmtoms in these patients. Patients may also present with visual impairment and symptoms of panhypopituitarism. Here, we present a case of endometrial carcinoma with pituitary metastasis.
Case
71-year-old female presented with a one-week history of loss of apetite and nausea. When questioned, she also reported headache and mild polyuria. One week before admission, she developed gradual right palpebral ptosis, diplopia, and progressive deterioration of vision. Her initial cranial MRI revealed 17×17 mm contrast-enhanced sellar tumor and brain edema. The main differential diagnosis of the sellar mass was pituitary metastasis of malignancy. The patient admitted initially to Neurology Department. On admission, her physical examination was normal except for the low blood pressure and right palpebral ptosis. Her ophtalmologic examination confirmed third nerve palsy. She had a history of endometrial serous carcinoma diagnosed in 2017, and she had undergone total histerectomy,bilateralsalpingo-oophorectomy, bilateral pelvicand para-aorticlymph nodedissection and omentectomy. After six cycles of paclitaxel-carboplatin, 18F-fluorodeoxyglucose (FDG) positron emission tomographic/computed tomographic (PET/CT)revealed liver and bone metastasis. She received six cycles of bevacizumab and doxorubicin, and she was on remission until her follow-up visit in June 2019. Routine laboratory evaluation showed a mild hypernatremia (Na=151 mEq/l) and low urine density (1005). Initial pituitary hormonal assessment demonstrated panhypopituitarism. Hypernatremia, low urine density and osmolality were compatible with diabetes insipidus. She was immediately treated with steroids, levothyroxine and desmopressin after the diagnosis. In subsequent days, her sodium levels were back to normal and urine output decreased. An 18F-FDG-PET-CT confirmed pituitary metastasis. Unfortunately, the patient was lost a week later due to extensive tumor burden. An autopsy was not performed.
Discussion
In conclusion, we present a case with sellar mass,ophthalmoplegia, headaches, hypopituitarism, mild diabetes insipidus, and known history of malignancy; imaging studies revealed pituitary metastasis. To the best of our knowledge, this is the second case of pituitary metastasis of endometrial carcinoma. Sudden onset of diabetes insipidus and ophtalmoplegia in a patient with known history of malignancy should raise the suspicion of pituitary metastasis.

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AEP706

Microprolactinoma, PCOS Or stress induced hyperprolactinemia? – case report

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Hyperprolactinemia is one of the most common problems in clinical endocrinology. It relates with various etiologies (physiological, pharmacological, pathological), the clarification of which requires careful history taking and clinical assessment.
We present the case of a 15-year-old girl, with history of secondary amenorrhea and headache in the presence of mildly elevated prolactin level, diagnosed as a microprolactinoma on MRI scan (4–5 mm) and treated with cabergoline (1 mg/week) for 2 years. At presentation she had resumed menses with low prolactin. Cabergolinewas stopped for 5 months,while she remained asymptomatic, with monthly menstrual cycles induced by progesterone. Biochemistry revealed: normal thyroid function tests, hyperprolactinemia: 4 × ULN (1229 uUI/ml) with equivocal reduction after PEG-47%), normal estradiol, low gonadotropes, normal IGF-1, normal urinary free cortisol, normal 17-(OH) progesterone and normal testosterone level. Pelvic ultrasound showed normal aspect of the ovaries. Sequential Pituitary MRI (2017): incidentaloma 4–5 mm; 2018: microadenoma (5–6 mm), (2019) stationary lesion of 7 mm after 2 yrs of cabergoline. The etiology of the elevated prolactin and of the secondary amenorrhea is challenging in this case, also the need of cabergoline treatment. Most guidelines propose in case of normal prolactin levels and no visible tumor remnant on MRI, after 2 years of low dose cabergoline, to try to stop medication. In this case, the presence of stationary, but visible pituitary microadenoma on MRI and resumed hyperprolactinemia after cabergoline cessation, could be indicative of either stress induced or tumor-secreting PRL, but there is no clear cut-off value of serum PRL level that could be usedto distinguish between them. Dimitriadis G *et al.* proposed the cutoff of PRL level exceeding 85.2 ng/ml in women with PCOS that is suggestive of a PRL -producing adenoma. In addition, pituitary MRI could be justifiable in young PCOS patients with milder PRL elevation, low LH levels and concomitant symptoms suspicious of a pituitary adenoma (Dimitriadis G, Angelousi A, Mehta H, Shad A, Mytilinaiou M, Kaltsas G, et al. The value of PRL in predicting prolactinoma in hyperprolactinemic PCOS. European Journal of Clinical Investigation. 2018;48:e12 961). In our case,the absence of PCOS criteria is limiting our possibilities to use this threshold. We will discuss the differential diagnosis and management of this unusual case.

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AEP707

A prolactinoma of rare localization as part of familial isolated pituitary adenomas

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Introduction
The syndrome of familial isolated pituitary adenomas (FIPA) or predisposition to pituitary adenomas (PAP) is characterized by the presence within the same family of at least 2 isolated pituitary adenomas without any other type of associated endocrine tumor. We report the case of a prolactinoma attached to the pituitary stalk as part of FIPA, revealed by erectile dysfunction.
Case report
A 40 year old man presented with eretile dysfunction since the age of 19. The investigations revealed a hyperpr *et al.* olactinemia at 289 ng/ml, a normal IGF1 for the age, hepatic, renal function, calcium levels, and the rest of the pituitary showed no abnormality. Pituitary MRI revealed the presence of a 27 × 21 × 14 mm mass suspended from the pituitary stalk. In the presence of a family history of 2 paternel cousins treated for isolated prolactinomas the diagnosis of familial isolated pituitary adenoma was established.
Discussion
More than 200 families with FIPA have been described in the medical literature. These pituitary tumors may present as homogenous with the same tumor phenotype or heterogeneous with different patterns of pituitary tumor phenotypes (GH, Prolactine, ACTH secretion or non functioning pituitary adenomas) within the same kindred. Patients with FIPA are significantly younger at diagnosis and have significantly larger pituitary adenomas than matched sporadic pituitary adenoma counterparts. About 20% of FIPA have mutations in the aryl hydrocarbon receptor interacting protein gene (AIP) usually associated with a worse outcome. Genetic study was not feasible at our level.
Conclusion
Familial isolated pituitary adenomas (FIPA) must be searched from anamnesis in front of any pituitary tumor and search by PCR (mutations of the AIP gene) given its prognostic interest. Our case is interesting not only by localization of the pituitary adenoma but also by the familial background.

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AEP708

A rare coexistence of acromegaly, myasthenia gravis, sicca syndrome, and elevated serum IgG4 levels: A single case report

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62-year-old woman was an employee of catering service. She had progressive limb weakness, easpecially proximal part since May, 2015, with diurnal change. She had difficulties in lifting arms, holding plates steady, and knee buckling while walking, which made her quit the job. Generalized myasthenia gravis (MG) was confirmed by positive acetylcholine receptor antibody (12.8 nmol/l) and marked decremental changes in repetitive stimulation test in November, 2015. Her limb weakness was much improved under pyridostigmine treatment. Chest CT scan revealed no thymoma, but thyroid nodules were incidentally found. Thyroid function test was normal. Thyroid ultrasound showed bilateral multinodular goiter, and fine needle aspiration

cytology showed negative for malignant cells. Otherwise, persistent elevation of serum IgG4 (214–249 mg/dl) was incidentally noted since May, 2016. She had dry mouth and dry eyes, but denied pancreatitis or mass lesions. Laboratory evaluation showed elevated ESR (27 mm/1-hr), positive of anti-ENA antibody (Ab) and anti-SS-A (8.028 U/mL), but negative of other auto-antibodies (anti-TPO, TA, ANA, anti-SS-B/dsDNA/SM/RNP/SCL-70/CENP/Jo-1/Ribosomal-P). She started hydroxychloroquine and pilocarpine treatment for Sicca syndrome. In November, 2019, thickened lips and widened teeth space were noted, but she denied enlarged fingers or feet, enlarged tongue, snoring, or arthralgia. Blood test showed high serum IGF-1 (588 ng/ml) and hGH (8.19 ng/ml). 75g OGTT showed paradoxical response and non-suppressible of GH (nadir 9.47 ng/ml) after glucose loading, and acromegaly was confirmed. Sella MRI revealed a 1.0 cm well-defined, non-enhancing nodule at left aspect of pituitary gland. She received endoscopic transnasal transsphenoidal adenomectomy on 2020/12/30. Serum GH level on post-operative day 1 decreased to 2.2 ng/ml. She reported subjectively better feeling with less limb weakness after surgery. Follow-up laboratory test in January, 2020 showed normal thyroid and adrenal function, and slightly decreased serum IgG4 levels (200 mg/dl). MG is a chronic autoimmune neuromuscular disease. Patients with MG usually have a higher incidence of other autoimmune disorders. The association between acromegaly and MG is extremely rare. There were only two cases of GH-secreting adenoma in MG patients reported. There was no report of association between acromegaly and other autoimmune disorders, such as sicca syndrome or IgG4-related disease, except one study reported higher thyroid autoimmunity in acromegaly patients than normal population. However, the identification of anti-pituitary antibodies in patients with acromegaly and other types of pituitary adenomas in some studies may suggest a possible involvement of autoimmunity in pituitary tumorigenesis.

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AEP709

A case of cyclic cushing's disease – cortisol surfing; catching the cortisol wave!

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A 28-year-old woman presents with a one-year history of marked weight gain of 18 kg, increasing hirsutism and night sweats. Clinically, hyperandrogenism and Cushing's syndrome were suspected. A diagnosis of Polycystic ovarian syndrome was made based on Rotterdam criteria and Metformin was initiated. Initial testing for Cushing's syndrome demonstrated a high 24 h urinary free cortisol (306 nmol/l) with incomplete cortisol suppression on an overnight dexamethasone suppression test (cortisol 60 nmol/l).However, a follow up low dose dexamethasone suppression test (48 h cortisol <28 nmol/l) and repeat overnight dexamethasone suppression test (Cortisol 44 nmol/l) were normal, casting doubt on the diagnosis of Cushing's syndrome. Clinical suspicion for Cushing's syndrome remained high as she continued to gain weight and experienced cyclic symptoms of rapid weight gain, easy bruising and emotional lability, and for this reason, further investigations were carried out. Serial midnight salivary cortisol and cortisone measurements were elevated ranging 3.5–7.4 nmol/l (normal <2.6 nmol/l) and ranging 12.8–31.3 (normal <18 nmol/l) respectively. Later a follow-up overnight dexamethasone suppression test showed no suppressibility of cortisol (84 nmol/l). Cyclic Cushing's syndrome was now suspected. A pituitary MRI showed a 3 mm right sided microadenoma and inferior petrosal sinus sampling clearly excluded ectopicACTHsecretion. Endoscopic transsphenoidal pituitary tumour resection was scheduled and performed using Brainlab image guidance. A day 4 cortisol (<28 nmol/l) was consistent with surgical remission and hydrocortisone was started. Histology of the pituitary lesion showed clear features of a Corticotroph adenoma. A follow up six-week insulin tolerance test confirmed secondary hypoadrenalism (peak cortisol 112 nmol/l).Post-operatively patient symptomology has now resolved with a reduction of Cushingoid features over time. She is having periods every 28 days (previously 26 days) and has plans for pregnancy in the coming year. Cyclic Cushing's syndrome is a rare, difficult to diagnose, form of Cushing's syndrome. It is often overlooked and is characterised by a cyclic pattern of normal cortisol interspersed with episodes of hypercortisolaemia. Intercycles periods can range from days to months. With the advent of the obesity epidemic it is becoming increasingly important for clinicians to remain vigilant when clinical suspicion of Cushing's syndrome is high despite conflicting Cushing syndrome screening results. We recommend the use of various cortisol screening tests in a temporal fashion and make use of a symptom diary whenever Cyclic Cushing's syndrome is suspected as the Cortisol Wave can be easily missed!

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AEP710

Successful pregnancy in a woman with acromegaly treated with lanreotide

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Introduction
Pregnancy in an acromegalic woman is rare and generally safe, but tumor expansion may occur. As this is a rare occurrence, little is known about the optimum management of such patients during pregnancy. We present the case of a woman with acromegaly treated with Lanreotide during pregnancy
Case report
A 29-year-old woman with acromegaly underwent transsphenoidal resection of invasive pituitary macroadenoma in August 2014, without cure. In November 2014, the IGF-1 level was 889 ng/ml (n:117 –239) and Lanreotide 120 mg was administered (s.c) every 6 weeks. In August 2015, a pregnancy in the woman was confirmed for the first time in week 14 due to irregular, rare periods. Lanreotide therapy was discontinued. In September 2015, MRI was repeated because of headache, sweating and hot flashes. The enlargement of the tumor, especially in cavernoussinus, was revealed. Lanreotide was reintroduced. The symptoms were reduced. The rest of the pregnancy was uneventful. On 29 January 2016, the patient gave birth to a healthy 2650 g son who has developed normally to date. The birth weight of her older children, born before her diagnosis, was 3200 g and 3100 g.
Conclusions
1. Lanreotide therapy during pregnancy is safe.
2. Exposure of the fetus to Lanreotide throughout pregnancy does not induce any malformations but it can induce slight fetal growth retardation.

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AEP711

Isolated adrenocorticotropic hormone deficiency in a female with ectopic posterior hypophysis

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Introduction
Some endocrine disorders, including hypophysitis and isolated adrenocorticotropic hormone (ACTH) deficiency, are caused by an autoimmune response to endocrine organs. Previous data have also shown that isolated ACTH deficiency may be associated at least in part with a paraneoplastic syndrome. We present a rare case with isolated ACTH deficiency along with ectopic posterior hypophysis.
Case presentation
A 53-year-old woman (menopause 45 yo), non-smoker, with a history of Hashimoto thyroiditis with normal thyroid function, osteopenia and cholelithiasis presented with fatigue and weakness gradually increasing in the last two months. Laboratory tests showed low morning ACTH: 9.8 pg/ml (n.v. 7–64), cortisol: 3.1 μg/dl (n.v. 6.2–19.4), DHEAS: 11 μg/dl (35.4–256) and Testosterone: <2.5 nmol/l (20–130), increased FSH and LH levels due to menopause and normal TSH, PRL and IGF-1 levels. Plasma renin activity and aldosterone levels were also normal. A pituitary MRI was performed and showed an ectopic posterior hypophysiswithout other abnormalities. An abdominal CT revealed atrophy in both adrenals. Due to the history of autoimmune thyroid disease, IgG4and CBG levels were also estimated and found to be within normal range. The patient was treated with hydrocortisone per os and showed rapid improvement of her symptoms.

Conclusion
Although the pathogenesis of some autoimmune endocrine diseases has been elucidated, it remains obscure for most. Further evaluation for the pathogenesis of isolated ACTH deficiency is needed.

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AEP712

Thickening of the pituitary stalk: About 4 cases

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Introduction
Pathologies of the pituitary stem are very often revealed during diabetes insipidus. The introduction of MRI constituted, in this context, a major diagnostic contribution. We report 4 cases of thickening of the pituitary stem observations. These are 4 patients (3 women and one man) whose age varies from 30 to 47 years, the circumstances of discovery are represented by amenorrhea in women and polyuropolydipsic syndrome in men. Clinically, diabetes insipidus was found in 3 patients, a gonadotropic deficit in 2 patients, a thyrotropic deficit in one case and panhypopituitarism in one case. The etiological investigation made it possible to retain the diagnosis of sarcoidosis in 2 cases and the diagnosis of Langerhansian histiocytosis in a patient, it was negative in one case.
Discussion
The pituitary stem connects the hypothalamus and the pituitary gland. It consists of two parts: at the top, the infundibulum, in direct contact with the tuber cinerum, at the hypothalamic level, at the bottom, the pituitary stem itself, which is extended by the posterior lobe of the pituitary gland. In case of pathology of the pituitary stem, the clinical picture is dominated by the occurrence of diabetes insipidus. It's the most common mode of revelation. The thickening of the pituitary stem associated with diabetes insipidus can be observed in the event of tumor, granulomatous or inflammatory pathology. The etiological diagnosis of 'large pituitary stems' is sometimes very difficult. Tumor lesions should be considered first, especially in children or adolescents, as they condition the prognosis and treatment. In adults, inflammatory or granulomatous causes are more common. In the case of a large pituitary stem, completely isolated, simple monitoring, without histological evidence, can be offered (by renewing the MRI at 3–6 months). A very prolonged monitoring of the remote MRI is essential (annual monitoring), in the hypothesis of a histiocytosis with prolonged evolution or of a germinoma, in particular in the child and the adolescent.
Conclusion
The stem can be the target of various infiltrative, infectious and tumor pathologies. An exhaustive etiological investigation is essential to guide therapeutic managemen

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AEP713

Pregnancy and pituitary adenomas: A case series

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Introduction
Pituitary tumours may interfere with fertility and pregnancy may be uncommon in these cases, but some patients can conceive spontaneous. Also in pregnancy, due to the physiologic changes of the pituitary gland, gradual volume increase and cellular hyperplasia that target hormonal secretion, the evaluation of the pituitary function is very complex.
Clinical cases
We present 5 cases of female patients (24 – 35 years old) that were diagnosed with different pituitary tumours and conceived. 2 patients were with acromegaly, 1 of them with macroprolactinoma, 1 with with microprolactinoma and the last one with non-functional pituitary adenoma. All women conceived naturally. We report 6 pregnancies with a positive outcome out of a total of 9. The patients with acromegaly had macroadenomas, one of them had conceived before the biochemical diagnosis of acromegaly. The other patient had gonadotroph deficiency after transsphenoidal surgery and gamma-knife radiosurgery and substitutive therapy. She had a spontaneous pregnancy during the estroprogestative treatment. She had a decrease in IGF-1 during pregnancy which after pregnancy returned to pathological elevated values. The patient diagnosed with microprolactinoma had an early pregnancy failure before her diagnostic was established. The patient conceived (twin pregnancy) under treatment with dopamine agonist her disease was controlled, and it was stopped immediately after the confirmation of the pregnancy. Unfortunately due to major cardiac malformations of the foetuses pregnancy interruption was indicated. The patient with macroprolactinoma had conceived many years prior the diagnostic. After thediagnostic of macroprolactinoma she conceived under treatment with bromocriptine. The gynaecologist indicated pregnancy interruption. Due to the resistance under high doses of dopamine agonists the patient underwent 5 cycles of temolozolomide with good outcomes. She conceived again and the pregnancy outcome was good. The last patient from our series had a non-functional pituitary microadenoma and successfully conceived after several years of attempts. During pregnancy the hormonal profile showed elevated IGF-1 (2×upper normal limit), and GH slightly elevated, most likely due to the physiological changes in pregnancy. The pregnancy outcome was positive. During pregnancy hormonal follow-up was made using IGF-1, GH (assay with no distinction of pituitary GH versus placental GH, PRL (prolactin), visual field and pituitary imaging was performed after delivery.
Conclusions
Managing pituitary dysfunctions in pregnancy can be challenging. The indications are to stop any medications that control prolactin or GH hypersecretion during pregnancy. Patients with different pituitary disorders can have successful pregnancies, even in patients with uncontrolled hypersecretion.

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AEP714

Short stature in turner syndrome: Should we assess growth hormone secretion?

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Introduction
Short stature is a common feature in Turner syndrome. It is caused by haplo-insufficiency of the SHOX gene. Growth hormone deficiency does not occur in this disorder as confirmed by the normal GH response to stimulation tests. However, few cases of coexisting GH deficiency and Turner syndrome have been reported. We herein describe two cases of GH deficiency in patient with Turner syndrome.
Observation 1
A 20-year-old patient was referred for delayed puberty. Physical examination showed a short stature with a height of 1 m38 (< −4 s.d.), dysmorphic features and female external genital organs, with Tanner stage 3. Her bone age was inferior to 17 years. On hormonal investigations, she had a primary hypogonadism (elevated FSH and LH levels and a low estradiol level), a severe GH deficiency and a corticotropin deficiency. Genetic testing confirmed the diagnosis of Turner syndrome. The pituitary magnetic resonance imaging (MRI) was normal. The patient was put on hormone replacement therapy.
Observation 2
A 16-year-old patient was referred for delayed puberty. On physical examination, she had a body height of 1 m 37(< −4 s.d.), multiples nevi and female external genital organs with Tanner stage 1. Her bone age was 9 years. She had a primary hypothyroidism, a primary hypogonadism, a severe GH deficiency and a corticotropin deficiency. Genetic testing confirmed the diagnosis of a classical Turner syndrome: 45 × 0. The pituitary MRI was normal. The patient was put on hormone replacement therapy.
Conclusion
These two cases highlight the necessity of GH investigations in patients with Turner syndrome and a severe short stature (body height < −4 s.d.). In addition, GH deficiency testing should be performed in the presence of at least one deficiency in the hypothalamic-pituitary axis. GH treatment is recommended in Turner syndrome. However, there are no recognized treatment recommandations in case of coexisting GH deficiency.

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AEP715

Case of differential diagnosis in a patient presenting with paroxysmal arterial hypertension

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Arterial hypertension (AH) may be the initial clinical presentation of various endocrine disorders. An accurate diagnosis provides an opportunity to achieve a cure of AH in some cases. Female patient, born in 1971, was referred to endocrinologist in 2018, at the age of 47 y, presented with AH and adrenal adenoma. Since the age of 35 y (2006), after the third delivery she had been suffering from AH with paroxysmal BP surges up to 180/120 mmHg, accompanied by panic, anxiety, sweating, tremor, palpitations, urge to urinate or defecate. Repeated urine catecholamines and metanephrines tests as well as adrenal US images were unremarkable. She had been followed by cardiologists with diagnose of hypertensive disease (paroxysmal hypertension). Despite regular taking 2–3 antihypertensive medications the paroxysmal attacks repeated occasionally. In 2017 the left-sided 17×14 mm adrenal mass (adenoma?) was found on CT and in 2018 she was referred to endocrinologist. Careful examination revealed moderate central body fat redistribution, normal BMI, rounded face and facial redness (though patient denied any significant changes in her appearance). No striae, easy bruising, hirsutism or thinning of the skin were found. Laboratory tests demonstrated normal 24-h urine metanephrines, 24-h urine free cortisol, plasma electrolytes, glucose, TSH, prolactin, renin and aldosterone, but increased ACTH level of 68-71-99 (normal<46) pg/ml, increased late-night salivary cortisol- 17,1 (normal<9.4) nmol/l and no suppression of plasma cortisolafter 1 mg overnight dexamethasone test. At the same time 4×4×2 mm microadenoma on pituitary MRI and osteopenia had been detected. The diagnosis of ACTH-dependent endogenous hypercortisolism (Cushing's disease) was established. Retrospective analysis of patient's medical history had revealed that in 2008 ACTH elevation up to 81.8 (normal≤63.3) pg/ml was detected, but the subsequent retesting had shown ACTH at the upper level of normal range. In 2012 and 2014 no microadenoma was clearly identified at the pituitary MRI. In 2019 the transsphenoidal resection of microadenoma was performed and Cushing's disease was histologically confirmed. After surgery BP and ACTH levels had returned to normal, and the paroxysmal attacks have not been recurred up to date. The non-typical features of this case comprise long duration of undiagnosed endogenous hypercortisolism with only manifestation of paroxysmal AH, inconsistent laboratory results, slow progression of rather modest signs of Cushingoid appearance, formation of unilateral adrenal mass. All these characteristics, more closely resembling the clinical picture of pheochromocytoma, could be misleading for cardiologists and resulted in the delayed correct diagnosis.

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AEP716

A rare case of panhypopituitarism caused by TNF-α inhibitors

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Aim
To present an unusual case of hypophysitis caused by TNF-α inhibitors and demonstrate the importance of astuteness with regards to endocrine axes testing when clinical circumstances indicate.
Case
A 78-year-old gentleman with known fistulating Crohn's disease (treated with adalimumab and infliximab in the past) presented with vomiting, dizziness, hyponatraemia and hypotension in early December 2018. SST showed he was cortisol-deficient, initially attributed to a right-sided adrenal haemorrhage (abdominal CT), as a result of previous ileal resection surgery.
In mid-December 2018, he was readmitted with diurnal and nocturnal polydipsia and polyuria and was subsequently diagnosed with diabetes insipidus. Further endocrinological testing revealed secondary hypogonadism and secondary hypothyroidism; low ACTH levels in combination with low cortisol levels confirmed secondary hypoadrenalism. Sequential MRIs raised the possibility of hypophysitis, which was further supported by the subsequent resolution of the inflammatory changes. He is currently receiving appropriate replacement therapy. Due to lack of precipitating factors or relevant past medical history, hypophysitis was attributed to a late effect of either adalimumab or infliximab.
Conclusions
This case highlights the importance of checking the integrity of different endocrine axes in light of an unexpected hormonal deficiency. Moreover, whilst it is well-known that immune checkpoint inhibitors, such as ipilimumab or nivolumab, can cause hypophysitis, it appears that TNF-α inhibitors can have a similar effect; the exact mechanism, though, remains to be elucidated.

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AEP717

Natural course of incidentally found nonfunctioning pituitary macroadenoma

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Introduction
The widespread use of neuroimaging leads to the increased detection of asymptomatic pituitary adenomasnot causing significant mass effect. Their optimal management remains unclear.
Aim of the study
To explore the natural course of incidentally found nonfunctioning pituitary macroadenomas.
Patients and methods
This was a longitudinal study that enrolled patients with clinically nonfunctioning pituitary macroadenomas who weren'tinitially referred to surgery either because of the relatively small tumor size or due to the increased surgical risk. Pituitary tumor size was regularly monitored with MRI. Significant increase/decrease in tumor size was defined as the increase/decrease of at least>3 mm in tumor diameter.
Results
The study included 41 patient (15 males, median age 59 years). Median tumor size was 15 mm (11–45 mm) in the largest diameter. Median follow-up was 36 months (range from 6 to 78 months). During follow-up, three patients were referred to surgery of whom only one had significant tumor growth. In 9 patients tumor size decreased, in 5 tumor size increased (only one of them needed surgical treatment) and in the remaining 27 patients no significant change in tumor volume was detected during follow-up.
Conclusion
The results suggest that it is quite unlikely for the initially asymptomatic nonfunctioning pituitary adenoma to undergo clinically significant increase in its size. It speaks in favor of the conservative approach in the management of that group of patients.

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AEP718

Evaluation of early predictors of metabolic syndrome in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NET)

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Metabolic syndrome and obesity (MetS) are supposed to have a role in cancer but data analysing their association with GEP-NET are lacking. Aim of this study was to explore the association of early predictors of MetS with GEP-NET, usingas tools Fatty Liver Index (FLI), a predictor of non-alcoholic fatty liver disease (NAFLD)and Visceral Adiposity Index (VAI), a gender-specific indicator of adipose dysfunction. A cross-sectional case-control observational study was conducted. VAI and FLI were calculatedin GEP-NET patientsreferred to the ENETS Center of Excellence of Naples, Endocrinology Unity of Federico II University between January 2015 and November 2019, as well as control healthy subjects, age, sex and BMI-matched. VAI isbased on waist circumference (WC), body mass index (BMI), triglycerides, and HDL cholesterol levels. FLI isbased on BMI, WC, triglycerides and GGT. We enrolled 103 patients with histologically confirmed G1/G2 GEP-NET (53 M, 50 F; 57.06 ± 15.95 years). GEP-NET were G1 (60%), G2 (40%) and metastatic in 26%. Differences in VAI and FLI were observed in GEP-NET patients compared with 103 controls. GEP-NET had a higher value of VAI and FLI compared with controls($P < 0.001$). These differences were associated to GEP-NET aggressiveness. Both VAI and FLI were higher in G2 than in G1 ($P < 0.007$, $P < 0.002$ respectively), and in metastatic vs non metastatic ($P < 0.001$, $P < 0.005$ respectively). In addition, higher value of VAI and FLI were significantly correlated with progressive disease ($P < 0.001$). This is the first study reporting an association between early predictors of MetS, VAI and FLI, and GEP-NET. VAI and FLI may represent a tool of evaluation in all conditions in which overt MetS is not present in GEP-NET.

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AEP719

Experience in complex therapy of selective and non-selective dopamine agonists in women with resistant prolactinomas for recovering of ovulation function

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Experience in complex therapy of selective and non-selective dopamine agonists in women with resistant prolactinomas for recovering of ovulation function.

Introduction

Prolactinomas are the most common pituitary adenomas and dopamine agonists (DA) still remain the first choice of treatment. Nevertheless, it does not always exert an adequate effect and endocrinologists face the challenge of resistant prolactinomas more frequently. This problem is very important for women who desire to become pregnant. In view of this fact, the search for a new ways for overcoming medical resistance becomes one of pressing issues in endocrinology. We present two clinical cases of women with DA-resistant prolactinomas, which successfully conceived after addition of bromocriptine to stable long-term high-dose cabergoline treatment.

Clinical case #1

A 26-year old woman presented with menstrual disturbances since 15 years old, secondary amenorrhea, galactorrhea for 3 past years. Clinical examination revealed hyperprolactinemia (PRL 10 000 IU/l, no macroprolactinemia), endosellar macroprolactinoma (10 × 11 × 12 mm) without visual disturbances, hypoplastic uterus. Administration of carbegoline with maximum dose 3,0 mg per week didn't result in significant clinical or laboratory improvement. The further increment of cabergoline dose was not possible due to patient's socioeconomic problems. However, the recovery of menstrual function and decrease in prolactin level to 1800 IU/l was observed after complex therapy of selective and nonselective DA (cabergoline 3.0 mg/week and bromocriptine 8 mg/day). And after 3 months of the therapy the patient naturally conceived. No pregnancy, delivery or fetus-associated complications were noted. She had a term delivery of a girl, weight – 3000 g, length – 50 cm.

Clinical case #2

A 27-year old woman presented amenorrhea, prolactin level was 13 146 IU/l, by MRI microprolactinoma 8*8 mm was detected. The therapy with cabergoline was started in dose 0.5 mg per week with escalation to maximum dose 4.5 mg per week. Despite treatment menstrual disturbance were persisting and prolactin level decreased to 2010 IU/l. Ultrasound examination revealed normal follicular count without signs of ovulation. The patient was recommended to add to the therapy bromocriptine in dose 2.5 mg per day. In two months, the patient got pregnant without recovering of menstrual function. Nowadays clinical examination on 26 gestational week did not present any fetal problems.

Conclusion

These clinical observationsdemonstrate an overcoming medical resistance to DA and achievement of natural pregnancy in patients with resistant prolactinoma using combination of selective and non-selective DA.

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AEP720

An analysis of craniopharyngioma patients in malta: Epidemiology, patient characterisation and long-term sequelae

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Background

Despite being benign, craniopharyngiomas are challenging tumours to manage and can cause significant morbidity and mortality in both the paediatric and adult population.

Method

Our aim was to analyse epidemiology, patient characteristics and long-term sequalae through a population-based study in Malta. A thorough research was carried out to identify patients who were diagnosed with craniopharyngioma in our local population. Subjects were identified from various hospital databases. Presenting features, patient and tumour characteristics, treatment modalities, long-term sequelae and epidemiology were analysed.

Results

From a cohort of 29 patients, 62.1% were male. The mean age at presentation was 32.4 years (s.d. ± 19.0). 11 patients (37.9%) were diagnosed with childhood onset craniopharyngioma (age at presentation < 20 years) whilst 18 patients (62.1%) had adult-onset craniopharyngioma. Median follow up period since time of diagnosis was 13.0 years (IQR 5–25). For incidence estimates, 13 patients who were diagnosed between June 2008 and June 2019 were included. The background population formed 4.8 million patient-years at risk. The overall SIR was 3.0/1,000,000/year, with the highest SIR in the 10–19 year age group. The estimated prevalence rate was 52.7/1,000,000 people, with lower prevalence rates for childhood- compared to adult-onset (20.3/1,000,000 vs 32.4/1,000,000 people). Visual disturbances and symptoms secondary to raised intracranial pressure were the commonest presenting complaints. Most tumours were multi-cystic (42.9%) and were commonly located in the intrasellar region with suprasellar extension. The median longest tumour diameter was 31.0 mm (IQR 21–41), with statistically significant difference between childhood- and adult-onset disease; 43.0 mm (IQR 42.5–47.25) vs 27.0 mm (IQR 20.55–31.55) ($P = 0.011$). All 24 patients who underwent neurosurgical intervention (82.8%) had adamantinomatous craniopharyngioma. 58.6% of patients required radiotherapy. The commonest long-term sequalae were hormone deficiencies (93.1%), followed by obesity (20.7%). Most patients required hormonal supplementation of more than one pituitary axis. 7 patients (30.4%) had evidence of tumour regrowth or recurrence during follow-up. 3 patients passed away throughout their follow up.

Conclusion

This study enabled us to obtain important data on the epidemiology of craniopharyngiomas, which was previously lacking. It also enabled us to better characterise these tumours and their long-term sequelae, broadening our knowledge with an aim to improve the patients' quality of life.

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AEP721

Septo-optic dysplasia with late-onset diagnosis: An uncommon presentation of a rare disease

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Background

Septo-optic dysplasia (SOD), also known as de-Morsier syndrome, is a rare congenital disorder characterized by any combination of optic nerve hypoplasia, pituitary dysfunction and midline abnormalities of the brain. Clinical diagnosis requires the presence of at least two of the features. This disorder is equally prevalent in males and females, with a reported incidence of 1/10,000 live births. There is wide variation in the severity of the clinical features found. The most common endocrine anomaly is GH deficiency followed by ACTH and hypothyroidism.

Case report
A 37-year-old man with complaints of chronic back pain performed a CT scan of the spine which revealed diffuse bone demineralization. Later, a DEXA scan confirmed the diagnosis of osteoporosis. Subsequently, laboratory studies were requested and a low testosterone level was identified. No relevant medical or family history. He did not have children. He denied asthenia or decreased libido. The patient presented normal body hair distribution, no gynecomastia, normal testicular volume, 79 kg and 173 cm. An evaluation of the pituitary axis confirmed a low testosterone level (155 ng/dl), with gonadotropins in the low normal range (FSH 2.7 UI/l, LH 2.2 UI/l), suggestive of central hypogonadism. TSH, Prolactin, ACTH, Cortisol, GH and IGF-1 levels were within the reference range. A brain MRI was requested and reported an absent septum pellucidum, thinning of the corpus callosum and underdevelopment of optic nerves, features compatible with septo-optic dysplasia. He was referred to an ophthalmologist yet no macula or optic disc defects were found. The patient started testosterone replacement therapy with good biochemical response. After the diagnosis, he fathered a child with a diagnosis of Costello syndrome. Both parents were then referred to the Genetic Department.
Discussion
Patients with SOD are often diagnosed during infancy with visual, neurologic or endocrine defects. The few adult patients reported in the literature were diagnosed due to drug-resistant epilepsy. Our patient was asymptomatic, thus the diagnosis was made during a clinical investigation for secondary causes of osteoporosis. The sole endocrine anomaly found was gonadotropin deficiency, the least common reported. Nonetheless, the diagnosis of SOD was based on the classic features presented on MRI.
It is curious that father and child were diagnosed with rare congenital diseases. Costello syndrome is characterized by short stature, developmental delay and a characteristic facial appearance. Only about 350 affected individuals have been reported worldwide. As far as we know, no relation between the two diseases have been described.

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AEP722

Doses of tolvaptan needed in chronic therapy of SIADH-induced euvolemic hyponatremia vary according to the etiology of SIADH

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Introduction
Clinical trials indicate that Tolvaptan is safe and effective in the treatment of patients with sustained mild/moderate SIADH-induced euvolemic hyponatremia. Tolvaptan doses are often modified during chronic use. We present the weekly doses of a series of patients on chronic therapy, followed up in outpatient clinic.
Methods
Retrospective, cross-sectional. 114 patients receiving tolvaptan for chronic SIADH were followed up in a Hyponatremia outpatient clinic in a tertiary hospital, initiating therapy between 2011 and 2019. Therapeutic goal: euvolemia, and serum sodium (SNa) 138–140, inmmol/l. Patients were instructed to drink freely when thirsty, and during meals. Salt was freely added to diet. Tolvaptan doses were modified as follows: increased 7.5 – 15 mg/day if patients were euvolemic with SNa ≤ 136, without polydipsia. Doses were lowered 50% when SNa > 140 mmol/l, patients presented thirst, polyuria, or low central venous pressure (maximum height of the internal jugular vein pulse below the sternal angle).Classification according to etiology of SIADH/additional diagnosis, for comparison of weekly doses: medication-induced (interruption of medication not viable) (MED), idiopathic SIADH of the elderly (IDIO), non-oncological pulmonary disease (PULM),neurological/neurosurgical disease (NEURO), oncological ectopic SIADH (ONCO), patients with chronic SIADH of diverse etiologies and prior episodes of heart failure (HF), and OTHERS. Weekly doses, mg, compared among groups. [Interquartile range].
Results
66 (57.9%) women. Median age: 76 [65–83.3]. Mean Pre-tolvaptan Nadir SNa: 121.1 (s.d.:5.86). MED: 22/114 (19.3%) patients, IDIO: 25/114 (22%), PULM: 17/114 (14.9%), NEURO: 9/114 (7.9%),ONCO: 13/114 (11.4%), HF: 6/114 (5.3%), others: 22/114 (19.3%). Median months therapy: 11[5.3–33.5], 45[20–61], 27[12.5–61] months, 7 [4.5–20.5], 10 [7–26.5], 46 [20.8–69.8], 21.5 [10.5–38] respectively.
Final median doses were significantly lower than at start in MED: 26.25 [22.5–52.5] vs 105 [52.5–105] ($P<0.001$), IDIO 26.25[22.5–52.5] vs 105 [52.5–105] ($P<0.001$), PULM 26.25 [26.3–105] vs 105 [78.8–131.3] ($P=0.019$), NEURO 26.25 [0–65.62] vs 105 [52.5–105] ($P=0.002$), OTHERS 52.5[26.25–105] vs 105 [52.5–210] ($P=0.006$).
Final median doses were significantly higher in ONCO: 105 [52.5–262.5] than in MED: ($P=0.001$), IDIO ($P<0.001$), PULM ($P=0.043$), NEURO ($P=0.012$), OTHERS ($P=0.017$).
There was no correlation between pre-tolvaptan nadir SNa and final doses.
Mean nadir SNa during tolvaptan therapy: 135.35 (s.d.:2.85). Mean maximum tolvaptan SNa: 141.04 (s.d.:1.8).
Side effects
No patient presented hypernatremia, nor liver-enzyme elevation. Thirst and/or polyuria were indications for lowering dose.
Conclusion
Chronic ambulatory tolvaptan therapy in SIADH is safe and effective. Doses can often be reduced, with the exception of oncology patients and SIADH patients with a history of heart failure. Eunatremia seems to be easier to maintain than to attain.

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AEP723

Soluble alpha klotho measurement: Comparison of measurements by different commercially available assays in healthy subjects and active acromegaly

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Background
Recent studies reported high soluble α-klotho concentrations (α-klotho) in active acromegaly, with normalization after successful therapy. We showed that α-klotho correlates to GH and even better to IGF-I. So far, most studies employed an immunoassay from Immuno-Biological Laboratories (IBL) for measurement of α-klotho, but other assays are available. Agreement between assays remains questionable since α-klotho exists in several isoforms: KL1-KL2 (shed by α-cut), KL1 (shed by β-cut) and truncated KL1 (synthesized by alternative splicing). In vitro studies suggest that IGF-I stimulatesα-klotho shedding.
Objective
Our aim was to compare measurements by assays that presumably differ in specificity for α-klotho isoforms in healthy controls and patients with acromegaly.
Methods
Circulating concentrations of solubleα-klotho were measured in 32 healthy controls and 22 patients with acromegaly by immunoassays from IBL and Immundiagnostik (IDK).
Results
α-klotho concentrations (pg/ml, median, interquartile) measured by IDK were ~8 times higher compared to IBL in healthy controls (6000 (4648–8681) vs 731 (558–899.7); $P<0.0001$), but only ~2 times higher in patients with acromegaly (11310 (6659–18172) vs 4809 (3048–10267); $P=0.0017$). Both Passing-Bablok and Bland-Altman showed greater disagreement between assays in all samples (Kendall's $\tau=0.04$ and 0.55, respectively). While the assays did not correlate in healthy controls (r Spearman=0.04, $P=0.83$), there was intermediate correlation in acromegaly (r Spearman=0.7, $P=0.0003$).
Conclusion
Results from both assays disagree dramatically. Lack of correlation suggests this is mainly caused by different recognition of isoforms rather than different standards. Since the KL1-KL2 isoform is equally detected by both assays, while the smaller shedding products are not, the better correlation in active acromegaly suggests that the proportion of the KL1-KL2 isoform increases in acromegaly. Furthermore, it is obvious that only results from studies using the same α-klotho assay can be compared.

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AEP724

Metformin and everolimus: A promising combination for neuroendocrine tumors treatment

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Treatment options for neuroendocrine tumors (NET), including everolimus, are rarely curative, as NETs frequently show resistance to medical therapy. In fact, the use of everolimus, an mTOR inhibitor, is limited by the development of resistance, probably due to the activation of Akt signalling. Metformin seems to have anticancer effects in neuroendocrine tumors (NETs). A recent retrospective study found longer progression-free-survival in diabetic pancreatic neuroendocrine tumor (P-NET) patients treated with everolimus and/or somatostatin analogs that were also taking metformin, irrespective of glycemic status, suggesting that metformin could have direct anticancer effects on NETs. Interestingly, metformin is able to inhibit mTOR and it also blocks the IGFR-1/IRS-1/PI3K/Akt cascade, providing the rationale for the use of metformin and everolimus in combination. We investigated the effects of metformin and everolimus alone and in combination on NET cell proliferation, apoptosis and colony formation, and the involvement of the Akt and mTOR pathways, also by developing everolimus resistant QGP1-R and H727-R cells. We demonstrated that metformin and everolimus in combination are more effective than monotherapy in inhibiting pancreatic-NETs cell proliferation, while no additive effects are observed on pulmonary-NETs cell proliferation. The combinatorial treatment is more effective than monotherapy in inhibiting colony formation and mTOR phosphorylation in both NET cell lines. We demonstrated that in QGP1 cells, metformin did not affect Akt phosphorylation; conversely, it significantly decreased Akt phosphorylation in H727 cells. Using everolimus resistant NET cells, we confirmed that metformin maintained is anticancer effects, acting by two different pathways: Akt dependent or independent, depending on cell type, both leading to mTOR suppression. Considering the promising anticancer effects of the everolimus and metformin combination in NET cells, our results provide the rationale for its use in NET patients.

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AEP725

One year of growth hormone therapy in spanish adults with prader-willi syndrome (PWS) improves body composition without changes in bone mineral density

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Introduction
PWS is the most common cause of genetic obesity. These patients have an abnormal body composition with increased amounts of fat mass (FM), reduced lean body mass (LBM) and diminished bone mineral density (BMD), all similar to patients with growth hormone deficiency (GHD).The abnormal body composition has been described due to impairment of the activity of GH-IGF system and to hypogonadism. Studies ongrowth hormone (GH) treatment in PWS adults from other European countries show improvement in body composition without changes in BMD.
Objectives
Our objective was to investigate the effect of GH on body composition in GHD genotype-positive PWS adults who had been under GH therapy for one year.
Design and patients
Twenty-seven PWS patients were diagnosed from GHD through two different stimulation tests: glucagon test and GHR+Harginine test[1]. At the time of the study, eighteen of them were undergoing sex steroid replacement therapy. Body composition was examined with DXA (Lunar Prodigy) before and after one year GH therapy. GH was initiated at 0.2 mg/day and adjusted depending on IGF-I values (values had to be at the upper part of the range). Total body water was estimated by bioelectrical impedance.
Results
Baseline body composition was: LBM 45.0±1.35%, 38.6±1.6 kg, total FM 54.4±1.34%, 48.9±3.0 kg. After one year of GH therapy, LBM increased significantly in 2.1% (*P* 25–75: 0.7–3, *P*=0.03), 3.1 kg (*P* 25–75: 0.04–6.2 kg, *P*=0.05), and total FM decreased also significantly in –1.6% (*P* 25–75: –0.5–2.7, *P*=0.005), –1.9 kg (*P* 25–75: –0.5–3.3 kg, *P*=0.01). Total body water increased in 0.5 kg, 0.7% (*P*=0.06). In relation to BMD, pre-treatment Z scores were lower than expected for age (lumbar spine *Z*–1.3±0.3 SD., total femur *Z*–1.2±0.24 SD.; femur neck *Z*–1.1±0.25 SD.). No significant changes were seen after one year of GH therapy. There was no correlation between the increase in IGF-I and changes in LBM and FM. No severe side effects were reported.
Conclusion
Our results are consistent with previous data and show that one-year treatment with GH in adult patients with PWS is safe, effectively improves body composition and does not change low bone mineral density.
Reference.
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AEP726

Efficacy and safety of urea in syndrome of inappropriate secretion of antidiuretic hormone on a secondary hospital

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Introduction
The most common cause of hyponatraemia is the syndrome of inappropriate antidiuretic hormone (SIADH). The diagnosis typically requires hyponatraemia in the setting of reduced serum osmolality, inappropriately concentrated urine with normal sodium excretion levels, and the absence of interfering medications, hypothyroidism and adrenal insufficiency. Unless hypertonic saline is indicated for acute onset profound hyponatraemia and/or with severe symptoms, the mainstay of management has traditionally been fluid restriction, a treatment often difficult to implement practically and effective in less than 50% of patients. Recent European and American guidelines differ in their approach to second-line management. Urea has been used for the treatment of SIADH since the 1980s but only few case reports/series have demonstrated it is an effective adjunct where fluid restriction is impractical or ineffective.
Objective
The objective of the study was to demonstrate that treatment with urea in patients with SIADH is a safe and effective alternative when fluid restriction has failed.
Methods
Treatment with urea (15 g/day) was started in all patients with biochimical diagnosis of SIADH (serum and urine natremia, plasmatic and urine osmolarity was determined) between 2016 and 2019. In all patients hypothyroidism and adrenal insufficiency was excluded. Results were analysed with SPSS v. 21.
Results
20 Subjects (55% men) were analysed with an average age of 77.05±15.4 years old, with biochemical diagnosis of SIADH. In our serie, the main cause of SIADH was drugs (50%), other causes were 25% paraneoplasia, 10% brain hemorrhage, 10% lung patology and 5% idiopathic. Initial natrium level was 124±3.8 mEq/l before treatment was started, with an average plasm osmolality 269±15.4 mOsm/l, urinary sodium 114±98,8 mEq/l, and urinary osmolality 484.6±235.56 mOsm/kg. Treatment with 15 g/day with urea was started with a median duration of 35 days, the natrium level was corrected in all patients, and it could be discontinued in 85% of them. The final average natrium level was 136.7±4 mEq/l, plasm osmolality 295.25±28.85 mOsm/l, urinary sodium 88.6±28.7 mEq/l and urinary osmolality 528.6±186.5 mOsm/kg. A rate mortality of 55% was observed, none of them due to SIADH.
Conclusions
Urea is safe and effective in fluid restriction-refractory hyponatraemia. We recommend urea with a starting dose of 15 g/day in patients with SIADH and moderate to profound hyponatraemia, as in our serie 100%, sodium levels were normalized and in 85% treatment with urea could be discontinued.

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AEP727

Multiple metastatic NET of unknown primary site in a young patient with carcinoid syndrome: Can we treat it as a gastrointestinal NET?

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Introduction
Neuroendocrine tumours (NETs) of unknown primary site are relatively uncommon, representing about 10% of all NETs. Of these, particularly the well-differentiated NETs often present initially with liver metastases, and most of these represent gastroenteropancreatic NETs. The presence of carcinoid syndrome is also common.
Case presentation
We describe the case of a 40 years-old patient presented in 2013 with flushing, diarrhea, and back pain. The chest-abdomen-pelvis CT showed several small lung nodules, multiple vertebral sclerotic bone metastasis, along with an osteolytic lesion on sacrum. It also revealed metastatic lesions in both hepatic lobes along with several enlarged abdominal lymph nodes. The upper and lower gastrointestinal endoscopy didn't show any lesion. A hepatic biopsy was performed, histopathological examination and immunochemistry showing well differentiated G1 NET, with Ki-67 < 3%, positive for chromogranin A, somatostatin receptor type 2 and 5 and also for CDX2, indicating a midgut origin. The serum serotonin, chromogranin A and urinary 5-hydroxyindoleacetic acid (5-HIAA) levels were elevated, thereby treatment with somatostatin analogues (SSA) was initiated, improving the carcinoid syndrome. The tumour markers had, however, an oscillating evolution (Table 1). For bone metastasis he received zoledronic acid and radiation therapy for pain control. A 99 mTc-Tektrotyd scintigraphy and SPECT/CT were also performed, still unable to showcase the primary site. Furthermore in December 2019, the patient has undergone the first therapy cycle of ^{177}Lu-DOTATOC peptide receptor radionuclide therapy (PRRT) and tolerated it well. The second cycle will be administered in February 2020.

Table 1 Serum Chromogranin A, Serotonin and urinary 5-HIAA/24 h levels during SSA therapy.

Date	5-HIAA mg/24 h (N: 2–9)	Serotonin mg/l (N: 80–400)	Chromogranin A mg/l (N: 27–94)	SSA	Dose of SSA/28 days
09.2014	242	1430	605	*Octreotide LAR*	20 mg
10.2015	118↓	2185↑	473↓	*Octreotide LAR*	20 mg
02.2017	149↑	>1000	540↑	*Octreotide LAR*	60 mg
07.2017	231↑	5.03↓↓	667↑	*Lanreotide AG*	120 mg
06.2018	285↑	3267↑	566 ↓	*Lanreotide AG*	120 mg
08.2018	97↓	1457↓	447 ↓	*Octreotide LAR*	60 mg
01.2019	165↑	2237↑	650 ↑	*Octreotide LAR*	60 mg
10.2019	145↓	1100↓	1320↑	*Lanreotide AG*	120 mg

Discussion
We showcase the importance of comprehensively investigating NETs of unknown origins as they are characterized by variable, yet frequently indolent evolution. Patients with abdominal masses on imaging scans and no evidence of the tumour on upper or lower endoscopy can be considered to have small intestinal primary tumours and should be treated according to guidelines.

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AEP728

A relationship between motilin and ghrelin in human motilin receptor transgenic mice

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Motilin (M), erythromycin (EM) and ghrelin (G) are recognized as important regulators of gastrointestinal motor function in humans that are mediated by class I guanine nucleotide-binding protein (G protein)-coupled motilin receptor (MR) and growth hormone secretagogue receptor (GHSR). These receptors have also been demonstrated as clinically useful pharmacological targets. However, a molecular relationship between MR and GHSR activation has been unclear. We generated human MR transgenic (hMR-Tg) mice because rodents do not endogenously express M and MR. In the current study, we examined gastric prokinetic effects, and relationship between M and G after administration of M, EM and G in hMR-Tg mice. M and EM affected concentration-dependent contraction of gastric smooth muscle in hMR-Tg mice but not in WT mice. Intraperitoneal (ip) and intracerebroventricular (icv) administration of EM significantly promoted gastric emptying in hMR-Tg mice but not in WT mice. The changes in gastric empty responses to EM icv administration were altered by atropin, but those to EM ip administration was not. G ip and icv administration significantly promoted gastric emptying in both hMR-Tg mice and WT mice. EM ip and icv administration reduced serum ghrelin concentration. According to our data, the hMR-Tg mice are useful for the evaluation of gastric prokinetic drugs in humans.

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AEP729

Characterization of epithelial-mesenchymal transition in growth hormone-secreting adenomas

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First generation somatostatin receptor ligands (SRL) are the first-line drugs in primary acromegaly treatment or after surgical failure in patients with active acromegaly. In previous studies we confirmed the association of the expression of *SSTR2*, Ki67 and E-cadherin (*CDH1*) in responsive GH-secreting adenomas response to SRL. Moreover, E-cadherin showed a greater predictive capacity than most of the markers described. Loss of E-cadherin is a typical mark of epithelial-mesenchymal transition (EMT) in solid tumors. Then, the objective of the subsequent work was to study the association of the EMT with the somatotropinomas response to SRL. We analyzed the expression of 8 genes related to EMT (*CDH1*, *CDH2*, *SNAI1*, *SNAI2*, *ESRP1*, *RORC*, *VIM* and *TWIST*) and other SRL response genes such as *SSTR2* and Ki-67 in 57 somatotropinomas (80% treated with SRL before surgery), using RT-qPCR. The results showed an expression pattern compatible with a EMT in 14% of tumors. When a cluster analysis was performed, epithelial markers (*CDH1*, *RORC*, *ESRP1*) clustered with *SSTR2* on one hand, and mesenchymal markers (*CDH2*, *SNAI1*, *SNAI2*, *VIM*, *TWIST*) with Ki-67. However, no clusterization of the tumors depending SRL response was found. The values of *CDH2* and *RORC* were higher in patients treated with SRL before surgery (F.C. = 3.14, $P = 0.02$, and F.C. = 2.39, $P < 0.01$, respectively). *SNAI1* and *RORC* showed differences, the latter only in SRL pretreated patients, between responding patients and resistant to SRL (HR = 2.03, $P = 0.05$ and HR = 0.59, $P = 0.01$, respectively). In addition, RORC levels correlated with the percentage decrease in IGF-1 after therapy with SRL (Pearson $r = 0.40$, $P = 0.03$).

Therefore, we conclude thatEMT occurs in some somatotropinomas, but it does not seem to explain their response to SRL in this subset of tumors. However, in the rest of somatotropinoma *SNAI1* and *RORC* may predict the response to SRL treatment.

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AEP730

Global methylation-demethylation status in pituitary neuroendocrine tumors as potential therapeutic target

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Background
The altered DNA methylation of certain genes in Pituitary Neuroendocrine Tumors (PitNETs) are well known. However little information is available regarding global methylation changes and the process of demethylation in these tumors. In addition, influencing global methylation-demethylation could be a potential new therapeutic option especially in clinically non-functional PitNETs.
Material and methods
Overall, 44 fresh frozen pituitary adenoma tissues (29 gonadotroph, 12 somatotroph, 3 corticotroph) were collected and characterized according to the 2017 WHO classification. Decitabine was used to alter global methylation-demethylation status on *in vitro* GH3 and RC-4B/B cell lines. In tissue samples 5-hydroxymethylcytisone (5 hmC), UHRF1-2 protein and Ki-67 were assessed by immunohistochemistry; gene expression of DNA Methyl-transferase (DNMT1), methyl-cytosine dioxygenases (TET1-3) and ubiquitin-like with PHD and ring finger domain (UHRF1-2) were investigated by RT-qPCR. 5-methylcytosine (5 mC) and 5 hmC level were determined by HPLC-MS/MS method.
Results
Decitabine decreased 5-methylcytosine (5 mC) and increased 5 hmC levels *in vitro* in both pituitary cell lines. Parallel, cell proliferation and viability were decreased significantly. UHRF1-2 were also altered upon decitabine treatment *in vitro*. Interestingly, in PitNET tissue samples 5 hmC was gradually decreased in samples with higher Ki-67 index. In samples with different histology UHRF2 showed different expression, while UHRF1 showed gradual increase in adenoma samples with higher Ki-67 index. Additionally, UHRF2 positively correlated with 5 hmC level in pitNET tissues and both UHRF1 and UHRF2 showed significant positive correlation with DNMT1 and TET1-3 expression.
Conclusion
Our results showed that methylation-demethylation process (5 hmC, DNMT1, TET1-3 and UHRF1-2) is closely linked to proliferative behaviour of PitNETs. Altering global 5 mC and 5 hmC level can be a potential, new therapeutic target in therapy resistant pituitary tumors.
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AEP731

The expression of oxytocin receptor (OXTR) in metastatic pancreatic neuroendocrine tumors (PNETs)

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Introduction
Pancreatic neuroendocrine tumors (PNETs) are rare malignant neoplasms which incidence is continually increasing. They are characterized by diverse biological behaviour and impact on the patients' prognosis, ranging from clinicaly indolent to very aggressive. Oxytocin receptor (OXTR) is a member of the family of G-protein receptors and is present on the cell-surface of the gastrointestinal organs. Unfortunately, theimpact of OXTR signaling on the development of PNETs and its underlying molecular mechanisms involved in gastrointestinal oncogenesis remains unsufficiently researched. Theaim of our study was to assess the expression of OXTR in a group of patients diagnosed with metastatic PNETs.
Material and methods
Metatatic PNETs (liver metastases) specimens ($n=24$) matched control (normal) tissue were surgically collected and mRNA expression was determined by Real-time polymerase chain reaction (Real-time-PCR). OXTR expression for tumor and control tissue was additionally analysed by immunohistochemistry.
Results
Compared to normal tissue, the OTXR showed significant overexpression in metastatic PNETs. Moreover, significant overexpression of OXTR in tumor tissue was confirmed by immunohistochemistry.
Conclusion
Our findings highlight the possibility of making OXTR a promising novel molecular target for imaging and different therapeutic approach in patients diagnosed with metastatic PNETs.

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AEP732

Metastatic insulinoma managed with lutetium (177LU) and somatostatin analog

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Background
Insulinoma is a rare tumour representing 1–2% of all pancreatic neoplasms and it is malignant in only 10% of cases. Locoregional invasion or metastases define malignancy, whereas dimension (> 2 cm), CK19 status, tumor staging and grading (Ki67 > 2%), and age of onset (> 50 years) can be considered elements of suspect.
Case presentation
We report a case of malignant insulinoma in a 80 year old woman presenting symptoms compatible with hypoglycemia. Low blood glucose levels (< 40 mg/dl) were documented during of these episodes. Symptoms regressed with food intake and intravenous glucose administration. No abnormality was detected in the biochemical evaluation. Prolong fasting test was performed, and the patient underwent symptomatic hypoglycemia at the 5th hour. Plasma glucose level was 39 mg/dl, insulin level 36.4 uIU/mL and C-peptide 9.28 ng/ml. Glucagon responce was measured 10 min. intervals, 85 mg/dl, 95 mg/dl and 113 mg/dl respectively. These results were suggestive of endogenous hyperinsulinemia. Magnetic resonance imaging revealed a invasive mass in the pancreatic tail location ~ 63×40 mm in size and multiple metastatic nodules in the the liver. Ga–68 DOTATATE PET-CT, which showed a lesion located in the pancreatic tail location and multıpl metastatic lesion in the liver, with a high somatostatin receptor density. Tru-cut biopsy made from liver lesions revealed the insulinoma tumour metastasis. Synaptophysin, pancytoceratine and chromogranin were positive. The histopathological diagnosis was suggestive of a neuroendocrine, grade-2 tumour (mitotic rate 1/10 HPF, KI-67 proliferative index 15%). Lanreotide 120 mg IM was started an every 28 days basis. The patient received 2 infusions of radiolabeled somatostatin analog lutetium (177LU) 8 weeks apart and denied any hypoglycemia. After the second administration of the lutetium, Ga–68 DOTATATE PET-CT had shown objective metabolic and radiologic response to treatment. Lutetium treatment was given as 8 cycles. Treatment of the patient with metabolic and radiological responses continues with lanreotide 90 mg/every 28 days.
Conclusions
We report a case of metastatic insulinoma treatment with somatostatin analog and Lutetium. Due to previous glycemic control reports and objective responses in unresectable cases, we decided to use Lutetium together with lanreotide. The patient's hypoglycaemia improved immediately after treatment. Unresectable metastatic insulinomas may present as a major therapeutic challenge for the physician. Treatment with landreotide and Lutetium

(177LU) seems to be effective in the management of severe, life-threatening, and refractory hypoglycemia associated with malignant insulinoma, as shown in the case presented here.

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Tobacco smoke induces aberrant pulmonary neuroendocrine differentiation via different MAPK pathways

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Tobacco smoke (TS) is the major cause of lung cancer, including pulmonary neuroendocrine tumors such as small cell lung cancer and large cell neuroendocrine carcinoma. Unlike squamous cell carcinomas and adenocarcinomas, the precursor lesions for subtypes of pulmonary neuroendocrine tumors have not been historically defined, and theexpression of neuroendocrine markers has been served as critical indices for the identification of these tumors. Mitogen-activated protein kinases (MAPKs) pathways play central roles in the development of cancer. To date, the role and regulation of MAPK pathways in TS-induced abnormal pulmonary neuroendocrine differentiation has not been elucidated yet. By employing long-term TS exposure of normal human bronchial epithelial cells and 12-weeks mouse smoking model approaches, in the present study we demonstrated that long-term TS exposure induced abnormal differentiation of human bronchial epithelial cells towards a neuroendocrine-like phenotype, as shown by increased cell proliferation, colony formation ability, invasive capacity, morphological change (from epithelial round-shaped to a neuroendocrine-like phenotype manifested by cell elongation and the emission of filopodia), and upregulated expression of pulmonary neuroendocrine differentiation markers including CgA, NCAM, SYN, and NSE. TS-induced aberrant pulmonary neuroendocrine differentiation was associated with MAPKs/AP-1 activation. Inhibition of EKR1/2 and p38 pathwaysdiminished TS-induced neuroendocrine differentiation in human bronchial epithelial cells. Furthermore, *in vivo* studies also revealed TS-induced neuroendocrinedifferentiation and MAPKs/AP-1 activation in mice. These effects were attenuatedby inhibition of p38 activation, but rather EKR1/2 and JNK pathwaysinhibition. Collectively, we illustrated the distinct roles of MAPK pathways in TS-induced abnormal neuroendocrine differentiation, among which p38 pathway serves as the pivotal player in this process. Findings from our study could provideimportant information for TS-induced aberrant pulmonary neuroendocrine differentiation, shedding new light on the carcinogenic process of TS-associated neuroendocrine lung cancers and its target intervention.

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AEP734

Use of tolvaptan in acute post-surgical hyponatremia in patients with pituitary diseases

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Introduction
Hypotonic hyponatremia is frequently observed after pituitary surgery. In this context, use of vasopressin V2-receptor antagonists is not standardized. The aim of this retrospective study is to explore the role of Tolvaptan in the management of acute hyponatraemia after pituitary surgery.
Methods
We collected clinical, safety and efficacy data of patients treated with Tolvaptan after pituitary surgeryin our Centre between April 2011 and February 2019.
Results
In 12 patients (8 women, median age 57.5 years) treated with Tolvaptan, hyponatraemia occurred in the 4th–7th post-operative day and was preceded by diabetes insipidusin 9 cases. In 5 patients the first line of treatment was 24 hours fluid restriction (range 6–36 hours), however the procedure was ineffective (median variation in sodium levels: –3, range: –8 to –1 mEq/l). Tolvaptan was administered in a single dose in 8 patients and in 2 doses in 4 [initial dosage: 7.5 mg ($n=5$), 15 mg ($n=6$), 30 mg ($n=1$)]. Median pre-Tolvaptan sodium was 125 mEq/l (range 112–129). One patient was mildly symptomatic, two patients had moderate symptoms and one severe. All patients were euvolemics. Twenty-four hours after the last administration of Tolvaptan, sodium was normalized in 9 out of 12 patients. Overcorrection (151 mEq/l) was observed in one patient, whereas mild hyponatremia persisted in 2. In two patients treated with a single dose of Tolvaptan, initial normalization of natremia was followed by further reduction in sodium levels (after 48 and 72 hours, respectively). No patient developed any side effects during Tolvaptan treatment. Correction rate was 12.5 (5 – 26) mEq/l/24 h after the first dose of Tolvaptan, and 11.5 (8 – 16) mEq/l/24 h after the second dose, with an absolute variation of natremia of +15.5 (7 – 26) mEq/l. No correlation between different doses provided and rate of correction was observed. Instead, overall variation of natremia was inversely proportional to the pre-treatment sodium levels ($P=0.02$). Overall, median length of hyponatraemia was 2 days (1.5 – 6).
Conclusions
Even at low doses, Tolvaptan is an effective and safe treatment for transient acute hyponatraemia in patients who underwent pituitary surgery, when fluid restriction is unable to determine an increase in sodium levels. In some patients, a single administration of Tolvaptan may not be sufficient and repeated administrations should be considered until hyponatraemia is resolved.

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AEP735

Metabolic status of patients with combined pituitary hormone deficiency due to PROP1 mutation

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Introduction
Combined pituitary hormone deficiency (CPHD) due to PROP1 mutation is a rare cause of childhood-onset pituitary disfunction. Treatment with growth hormone is crucial for the proper development during childhood and adolescence, and to maintain adequate metabolic processes in the adulthood. There are other factors influencing patients metabolism e.g. steroid and estradiol/testosterone treatment.
Aim
To assess metabolic status of patients with CPHD due to PROP1 mutation.
Methods
20/28 patients with PROP1 CPHD who are under medical supervision of the Department of Endocrinology (12 F/8 M; mean age [MA] 43.2±14.2) completed routine laboratory tests during 2019.
Results
In all patients GH, TSH and gonadal axes deficiencies were diagnosed. In 17/20 adrenal and 1/20 ADH deficiency was diagnosed. 9/20 (older patients) received (due to no compliance/other reasons): no/delayed/intermittent GH treatment in childhood. In adulthood 7/21 patients were intermittently treated with GH. 8/12 F and 8/9 M have received sex hormones supplementation. The sub-group of patients properly treated with HGH (t-HGH) in childhood consisted of 6 W/6 M, MA 33, 3±7.3 y, mean final height (MFH) 170.4±6.0 cm. In subgroup of patients not treatedwith HGH (nt-HGH) in childhood there were 6 W/2 M, MA 58.0±8.1 y, MFH 139.6±7.4 cm.
Combined analysis of all patients revealed that the most frequent disorders were hyperlipidaemia (65%), low bones mineralization (57%), vitamin D deficiency (50%), overweight (45%), visceral obesity (45%), hypertension (35%) and insulin resistance (35%).
The most common metabolic problems in nt-HGH were bone demineralization (100%), hyperlipidaemia (100%) and visceral obesity (75%) whereas in t-HGH low vitamin D concentration (50%), hyperlipidaemia (42%) and visceral obesity (42%).
In both group we have observed elevated markers of insulin resistance, however none of the patient met diabetes criteria.
Conclusions
Metabolic abnormalities are very common among patients with CPHD related to PROP1 mutation.
Metabolic changesand osteoporosis observed in young adults prove that even correct replacement therapy cannot prevent the health deterioration. Further investigation on understanding of metabolic disorders and setting

standards of care (e.g. treatment of osteoporosis in young adults) are needed. This specific group of patients needs an extensive care of multidisciplinary team of experienced endocrinologist, cardiologist, rheumatologist and dietician.

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AEP736

Kisspeptin levels in children and adolescents

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Kisspeptin (metastin, HH13, KiSS-1, KiSS-1 metastasis-suppressor, KiSS-1 metastasis suppressor) is a neuropeptid that is encoded by the KISS1 gene (Messager *et al.*, 2005). Kisspeptin-GPR54 signaling has an significant role in initiating secretion of gonadotropin-releasing hormone at puberty (K. Skorupskaite *et al.*, 2014). Is known that kisspeptin to play a role in tumor suppression (especially in breast tissue), (E.J. Mead *et al.*, 2007).

Objectives

To determine kisspeptin levels in healthy children and adolescents, in children and adolescents with endocrine and mammalogic diseases.

Patients and methods

Serum kisspeptin levels was determined in 123 children and adolescents (aged 0.7–18 yrs), in the 8 groups, including control groups. The healthy children was 12, healthy adolescents – 30, children with central precocious puberty (precocious puberty CPP and premature isolated the larche PT) – 11, girls with amenorrhea – 23, adolescent girls with dyshormonal mammary dysplasia – 12, patients with polycystic ovary syndrome (POS) – 9, pregnant adolescent girls – 15 and adolescents with gynecomastia was 11 boys. The concentration of kisspeptin was measured kisspeptin (total) using competitive enzyme immunoassay. Results were analyzed using Pearson's chi-squared test. Data are expressed as median, P value of <0.05 was considered statistically significant. This study was carried out in accordance with the Helsinki Declaration.

Results

The investigation shows that healthy and pregnant adolescent girls, boys with gynecomastia had kisspeptin median level was 30 pg/ml. Among the girls with amenorrhea kisspeptin level was lower 10 pg/ml ($P=0.01$). Girls with mastopathy (dyshormonal dysplasia) had kisspeptin level 50 pg/ml ($P=0.03$). Serum kisspeptin levels were significantly higher in children with CPP and PIT and adolescent girls with polycystic ovary syndrome than in control group (80 and 300 vs 30 pg/ml, $P=0.01$ and $P<0.01$).

Conclusions

Kisspeptin level was various in healthy children, girls with amenorrhe, mastopathy, polycystic ovary syndrome, premature isolated thelarche, children with central precocious puberty, pregnant adolescent girls and boys with with gynecomastia. In this study data received that serum kisspeptin level was significantly lower in girls with amenorrhea and higher in children with CPP and PT, girls with mastopathy and POS. Kisspeptin levels in girls with mammological diseases are statistically significantly higher, which can be explained by compensatory reactions in response to proliferation in mammary glandular tissue. The serum kisspeptin level may be used as a biomarker of sexual disorders, polycystic ovary syndrome and mammary diseases and in girls.

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AEP737

Body composition and bone mineral density in 107 patients with childhood onset growth hormone deficiency (CO-GHD) at the time of transition from pediatric to adulthood endocrine care

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Transition from childhood to adulthood is a vulnerable period in all adolescents and particularly inCO-GHD patients. Low bone mineral density (BMD) and body composition alterations are frequently reported in young adults with CO-GHD, but relevant large monocentric studies are lacking.

Patients and Methods

In a monocentric, observational, retrospective cross-sectional study conducted from 2005–2019, 107 CO-GHD patients were analyzed (17–26 years old, 80 males) at the time of transfer from pediatric to adult endocrine care. Median age at transfer was 19.6±2.2 years. Subjects withcongenital and idiopathic GHD (CON) were compared with age-, sex- and BMI-matched patients with hypothalamic/pituitary tumor history (TUM). Body composition (% fat, fat mass – FM and lean body mass – LBM) and BMD in lumbar spine (LS) and femoral neck (FN) – (BMD g/cm^2, Z score) were analyzed by DXA.

Results

Congenital and idiopathic causes of GHD were more frequent than hypothalamic/pituitary tumoral causes (74.8% vs 25.2%).All patients received GH replacement during childhood for average duration of 5.4±1.4 yrs. GH replacement was discontinued prior to transfer for 2.7±0.9 yrs. Recovery of GH/IGF-I axis was confirmed by retesting in 15.5%. Percentage of fat was significantly higher in TUM vs CON (30.1 vs 34.0 kg; $P<0.05$) and LBM was significantly higher in CON (46.2 vs 40.1 kg; $P<0.05$). BMD (g/cm^2) and Zsc in LS and FN were lower in TUM (> P 0.05) while FM was higher in TUM ($P>0.05$).

Conclusion

Patients with CO-GHD caused by hypothalamic/pituitary tumors demonstrated worse body composition and lower BMD at the time of childhood to adulthood transition compared to matched transition patients with congenital CO-GHD

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AEP738

Management of pregnant women with prolactinomas and analysis of their pregnancy outcomes

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The purpose of the study was to study the characteristics of the course of pregnancy and childbirth in women with prolactinomas, as well as the effect of pregnancy on the size and functional activity of prolactin-secreting pituitary adenomas.

Materials and methods

70 women with prolactinomas during pregnancy were examined. The age of the examined patients from 20 to 38 years (28.9±0.5 years). The duration of the disease ranged from 3 months to 20 years and averaged 2.8±0.2 years. The menarche age ranged from 11 to 18 years and averaged 13.2±0.2 years. A regular menstrual cycle before pregnancy was present in 6 (8.5%) patients with prolactinoma. Opsomenorrhea was present in 30 (42.8%) and amenorrhea 15 (21.4%). Before pregnancy, lactorrhea of I-II degree was present in 40 (57.1%) women, III degree – in 7 (10%) women. Pregnancy occurred during therapy with dopamine agonists. 6 (8.5%) patients underwent stimulation of ovulation with clomiphencitrate. Three (4.2%) women with macroprolactinoma had asymmetric bitemporal hemianopsia. 10 (14.2%) patients in the past underwent surgery on the pituitary gland. In 2 (2.8%) patients with pituitary macroadenoma, surgical treatment was combined with radiation therapy. Microadenomas were present in 51 (72.8%) patients, macroadenomas – in 19 (27.1%) women. The sizes of prolactin before pregnancy ranged from 3 mm to 42 mm (9.2±1.0 mm). The average tumor size in patients with pituitary microadenoma was 5.0±0.3 mm, with macroadenoma – 18.0±1.8 mm. The level of prolactin in the blood of patients ranged from 900 mIU/l to 10,000 mIU/l and averaged 3361.8±307.2 mIU/l.

Results

With microadenomas due to the low risk of tumor growth, observation without treatment is possible based on clinical symptoms. With macroadenomas, pregnancy must be planned to achieve control of tumor growth. Careful observation or treatment with dopamine agonists throughout pregnancy is preferred, depending on the particular patient. To minimize risks to the fetus, treatment with dopamine agonists should be started after the first trimester. Breastfeeding may be allowed, as there is insufficient evidence against this. Patients requiring dopamine agonists to prevent tumor growth should continue treatment, although lactation may be impaired.

Conclusion

Preference is given to careful observation or treatment with dopamine agonists throughout pregnancy, depending on the particular patient.

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AEP739

Interleukin-6 response to insulin-induced hypoglycemia is associated with hypothalamic-pituitary-adrenal axis activation

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Introduction
Increased plasma levels of interleukin-6 (IL-6) in response to acute hypoglycemia have been well documented. Counter-regulatory hormones are likely to play a role in this inflammatory response.
Objective
To study the interaction between IL-6 and counter-regulatory hormones during hypoglycemic stress.
Methods
We conducted an exploratory single center study involving 23 patients (mean age = 34.15 ± 8.87 years, $n = 12$ women) undergoing insulin tolerance test (ITT) for suspected pituitary dysfunction. Procedure-related symptoms of anxiety and hypoglycemia were measured using a standardized questionnaire. Blood levels of IL-6, adrenocorticotrophic (ACTH), adrenaline, noradrenaline, growth hormone (GH), prolactin and serum and salivary cortisol were determined throughout the ITT.
Results
Insulin-induced hypoglycemia was safely achieved in all subjects and elicited a significant dynamic response of ACTH, adrenaline, noradrenaline, GH, prolactin and serum and salivary cortisol ($P < 0.001$ for all variables). IL-6 plasma levels significantly increased after hypoglycemia ($P < 0.001$). The increase of plasma IL-6 levels during hypoglycemia correlated with the increase of serum cortisol ($rs = 0.46$; $P = 0.022$), salivary cortisol ($rs = 0.52$; $P = 0.021$), plasma ACTH ($rs = 0.47$; $P = 0.023$) and anxiety symptoms ($rs = 0.441$; $P = 0.004$).
Conclusion
Hypoglycemic stress-induced IL-6 increase is associated with the activation of the hypothalamic-pituitary-adrenal axis, reinforcing the concept that inflammatory response to stress may be regarded as a component of a broader counter-regulatory response.

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AEP740

The effect of dual-release versus conventional hydrocortisone on fatigue, measured by ecological momentary assessments

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Background
Replicating the physiological cortisol secretion is key in treatment of glucocorticoid insufficient individuals. A sub-optimal replication may explain the impaired quality of life experienced by these individuals. The study investigates fatigue measured by ecological momentary assessments in patients treated with conventional hydrocortisone compared with a once-daily dual-release formula of hydrocortisone (Plenadren) that follows the cortisol physiology more closely.
Methods
The 21-week open-label switch pilot trial included patients with adrenal insufficiency due to hypopituitarism ($n = 27$). While treated with their usual hydrocortisone regimen, fatigue was assessed four times daily for 20 days using a momentary item version of the Multidimensional Fatigue Inventory. Participants switched treatment to an identical daily dose of Plenadren. The intervention period was 16 weeks and was concluded with repeating the fatigue assessments for 20 days.
Results
On four out of five fatigue subscales, we found statistically significant yet modest treatment effects. Fatigue was reduced 0.7–1.1 points, on a scale ranging from 4–20, when treated with Plenadren compared with conventional hydrocortisone. Changes corresponded to small effect sizes but were below scale-specific minimal important changes. We found larger between-person variances and smaller within-person variances when treated with Plenadren. On an individual level, nine participants (one third) experienced improvements above the minimal important change whereas four participants deteriorated. The method of ecological momentary assessment could furthermore detect a significant diurnal curve of fatigue, and a visual change of the pattern between conventional hydrocortisone and Plenadren.
Conclusion
The Plenadren-related reduction in fatigue was significant but not necessarily of clinical importance when looking at group level. However, there was a large inter-individual treatment effect, why patients with great benefit in quality of life should be identified. Furthermore, the method of ecological momentary assessments was highly suitable for studying fatigue in this patient population.

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AEP741

Cushing's syndrome in the 21st century, not what it used to be: A single institution experience

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Background
True Cushing's syndrome (CS) is an exceedingly rare condition, thus to avoid unnecessary and costly testing, a diagnostic investigation should only start based on solid clinical suspicion. The current obesity epidemic has become a hurdle in discriminating subjects at real risk for CS from those with the metabolic syndrome. Moreover, many CS patientsrecently diagnosed do not fit the typical clinical profile of 'at risk subjects'.
Aim and Design
To characterize the clinical presentation of patients with confirmed CSat Tel Aviv Sourasky Medical Center between 2000–2018. Relevantclinical, laboratory, imaging and pathological datawere retrospectively retrieved and analyzed fromCS patients' charts.
Results
We identified 76 patients with CS (79%women) with a clear increased incidence over the years. The subtypes comprised: 49 Cushing's disease (CD) 64.5%, 16 benign adrenal process (BA) 21.1%, 7 ACC 9.2%, and 4 cases of ectopic ACTH secretion (ECT) 5.3%. Mean age was 47.9 ± 15.3 y (range: 18–79), by ANOVA ($P = 0.003$), CD subjects being significantly younger than subjects with ECT. Clinical suspicion of CS initiated a diagnostic work-up in only 15 subjects (19.7%). In 48 (63%), an investigation started either for incidental imaging or laboratory findings, or for nonspecificreasons(i.e obesity). Once the diagnosis was known, in 50% of the cases an endocrinologist noted the patient did not appear to suffer from CS. The most common co-morbidities were hypertension (62.7%), hyperlipidemia (48.6%), obesity (48.6%), osteoporosis, and diabetes (36.8%).The most common symptoms were muscle weakness in both genders (29.6%), and menstrual disturbances in women of reproductive age (46.8%). Acute weight gain was reported by only 17.1% of subjects. Finally, the most common signs were abdominal obesity (70%), buffalo hump (38%), and a round/moon face (37.5%). Typical striae were noted in only 20.8% of subjects. All these features were less frequent than usually quoted in the literature. We generated a disease severity score which was positively correlated with serum cortisol after an overnignt dexamethasone suppression test ($r = 0.42$, $P = 0.003$), but not with urinary free cortisol excretion.
Conclusions
Our tertiary institution's experience suggests the incidence of diagnosed CS is rising. Nonetheless, clinicians should be aware that the majority of modern era CS patients might escape diagnosis due their non-classical presentation. Our findings add further uncertainty as to which patients should be screened for CS.

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AEP742

Visual impairment in patients with pituitary apoplexy

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Introduction
Pituitary apoplexy (PA) is a rare incident defined by the occurrence of necrosis and/or haemorrhage of the pituitary gland. PA is a clinical syndrome

characterized by the sudden onset of headache, vomiting, visual impairment and decreased consciousness in some cases. The objectives of our study are to describe its clinical features and characterize the visual impairments in a cohort of PA in the region of Sfax.
Methods
It is a retrospective study including a group of patients in the Endocrinology department of Hedi Chaker Hospital in Sfax over an 18-year period (2000–2017). The data collected was analysed by the SPSS version 20 software.
Results
This study included 44 patients (20 women vs 24 men) with a mean age of 50.04±12.58 years. Fourteen patients (31.8%) had a pituitary adenoma known before the onset of apoplexy, secreting in 9 cases. Precipitating factor have been found in 14 cases (31.8%). At the time of apoplexy, an ophthalmological examination was performed in 34 patients only (77.3%). Visual loss was diagnosed in 10 patients (22.7%) who presented macroadeomas in all cases. A decrease in visual acuity was variable, ranging fromloss of some diopters (2 to 8) in 7 patients to a simple unilateral light perception in two cases and total blindness of one eye in one case. Bitemporal hemianopsiawas observed in 13 patients, and impairment of the visual field in 4 case. Papillary oedema was observed in 5 cases and a simple papillary pallor in 2 cases. Complete optic atrophy was observed in one case with a 2.5 cm macroadenoma and with compression of optic chiasm. The diagnosis of oculomotorpalsy was made in 9 cases (20.5%).Involvement of the common oculomotor nerve (III) was present in 7 cases (15.9%). Palsy of the pathetic nerve (IV) was noted in 4 cases. Palsy of theexternal oculomotor nerve (VI) was noted in both cases with total oculomotorpalsy.
Conclusion
The clinical picture of pituitary apoplexy is characterized by the sudden onset of oculomotor palsy or blindness with acute headaches and even consciousness impairment which need a fast intervention to prevent visual and life-threatening complications.

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AEP743

Central hypothyroidism as an adverse effect of bexarotene treatment for cutaneous T-cell lymphoma

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Introduction
Central hypothyroidism is rare, estimated to occur in 1:20,000 to 1:80,000 in the general population. Pituitary mass lesions and adverse effects of their treatment are the most common causes of central hypothyroidism. In recent years, the incidence of pituitary hormonal deficiencies as adverse effects of novel molecular targeting anticancer drugs has risen sharply. Especially checkpoint inhibitors are associated with partial or complete hypopituitarism. In this report, we describe a case of isolated central hypothyroidism as a side effect of the retinoid X-receptor-selective ligand (RXR) bexarotene, used for treatment of cutaneous T-cell lymphoma.
Case report
A 74-year-oldmale patient presented with skin changes accompanied by severe pruritus. A skin biopsy revealed a cutaneous T-cell lymphoma (Sézary syndrome). Due to progressive disease under the initial therapeutic approaches, a third-line therapy with bexarotene was initiated. Only six days after initiation of bexarotene, the levels of free thyroxine (fT4) decreased to 7.7 pmol/l (with a nadir of 6.5 pmol/l in the follow-up) and the level of thyroid-stimulating hormone fell to 0.104 mIU/l (with a nadir of 0.005 mIU/l in the follow-up). Upon initiation of levothyroxine substitution (initially 50 mg/d, later 75 mg/d), the levels of fT4 increased, but remained in the hypothyroid range. After increasing the dose to 100 mg levothyroxine/day, the fT4 normalized (12.3 pmol/l). The patient did not develop symptoms of hypothyroidism and there were no deficiencies of other pituitary hormones.
Discussion
Bexarotene is a ligand of the retinoid X-receptor, and central hypothyroidism belongs to its described adverse effects. Link between thyroid function and vitamin A metabolism has been first described in the early 1970s when central hyperthyroidism was found in rats with vitamin A deficiency. Supplementation with levothyroxine reversed this by suppressing TSH secretion. Bexaroten seems to exert its effect by forming a heterodimer with thyroid hormone receptor in peripheral tissue. In addition,it inhibits the transcription of TSH-β subunit independently of triiodothyronine and promotes the clearance of thyroid hormones, resulting in accelerated hypothyroidism. Therefore, an increased thyroid replacement dose may be warranted in patients with bexarotene-induced hypothyroidism

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AEP744

Pasireotide-induced hyperglycemia and efficacy of antidiabetic treatments in patients with acromegaly: Evaluation of two referral centers

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Pasireotide (PAS) has a safety profile similar to first-generationsomatostatin analogues (SSA), except for a higher frequency of hyperglycaemia-related adverse events (AEs). However, consensus on the best management of PAS-induced hyperglycaemia in acromegalic patients has still to be defined. The current study aims at investigating the effects of long-term PAS treatment on glucose metabolism, by evaluating the clinical management of hyperglycemia-relatedAEs in acromegalic patients followed in two Italian referral centers, participating to the PAOLA study. The role of metabolic parameters (weight, BMI, fasting glucose and HbA1c levels) and markers of disease activity (GH, IGF-I, duration of PAS treatment) were investigated as potential predictors of hyperglycemia development. A total of 31 patients (16 F/15 M, mean age 47.6 years) entered the study. Patients were treated with PAS for a mean time of 34 months (6–67). Glycemic control was established with HbA1c at 7%. During PAS treatment, mean FPG and HbA1c concentrations significantly increased ($P=0.005$) after 6 months of treatment, remaining persistently elevated until the last follow-up ($P=0.005$). At baseline, pre-existing diabetes mellitus (DM) was found in 6 (19%), and glucose intolerance (GI) in 4 (13%) patients. Hyperglycemia-related AEs, generally mild to moderate, were reported in 24 patients (77.4%, 5 worsening DM, 9 DM, 9 GI), occurring after a mean time of 6 months (1–17 months). One patient discontinued because of DM. At regression analysis, baseline glucose levels resulted aspotential predictors of hyperglycemia during PAS therapy ($P=0.04$, $r=0.25$). At study entry, 4 patients (13%) were already treated with antidiabetic drugs. Eight patients (33.3%) were treated only with hypocaloric diet for the study duration. Starting of new antidiabetic treatment was required in 12 patients (50%) throughout the study, and metformin (MET) was as first-line therapyfor all patients. Seven (58.3%) patients did not control glucose and HbA1c levels despite MET monotherapy, needing further therapies. MET was associated with DPP-4 inhibitor in 2 patients (16.6%), GLP-1 agonist in 3 patients (25%), GLP-1 agonist and glargine insulin in 2 patients (16.6%) patient to control hyperglycemia. Five patients (20.8%), 1 patient treated with MET (20%), 1 with hypocaloric diet (20%), 1 with MET and glargine insulin (20%) and 2 with insulin (40%) were uncontrolled at last follow-up. In conclusion, the results of the current study show a long-term effect of PAS therapy on glucose metabolism, but treatment with MET or its association with incretin resulted in good glycemic control in most patients.

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AEP745

The characteristic of patients with pituitary stalk lesions – single center,long term observation

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Background
Pituitary stalk lesions (PSL) is a general term used to describe changes located in the pituitary infundibulum. Special anatomical locus makes the diagnosis difficult to establish. Most of the patients with PSL characterizes with hypopituitarism and multiple metabolic abnormalities.
Aim
To present the characteristic of patients with PSL.
Methods
We analyzed data of 35 patients (21 M/14 W) with pituitary stalk lesions on the basis of long term observation in the pediatric/adult endocrinology departments of our university. Current metabolic data were available for 19 patients. The etiologies were divided into three groups (congenital, inflammatory, neoplastic) and classified as exact, probable or unknown.
Results
The mean age of diagnosis was 28 years (s.d. 24.26). The most common causes of PSL were congenital malformations (16/35, 45.7%), an inflammatory etiology was found in 13/35 (37.1%), while neoplasms were diagnosed in 6/35 (17.1%) of patients. The exact etiology was established in 24/35 (68.6%) cases (16 congenital malformations, 5 histiocytosis, 1 Erdheim-Chester disease, 1 germinoma, 1 hypophysitis). The probable cause was suggested in 7/35 patients (20.0%) – six with the suspicion of lymphocytic hypophysitis and one with a metastasis from a disseminated neuroendocrine cancer. The origin of 4/35 PSL (11.4%) remains unknown. During hormonal assessment the most common insufficiency concerned the thyroid axis, found in 18/35 (51.4%) patients, followed by somatotropic (17/35, 48.6%), gonadal (15/35, 42.9%) and adrenal axis (11/35, 31.4% of cases) insufficiencies. 12/35 (25.7%) patients were diagnosed with diabetes insipidus. Some deficits were transient. Obesity/overweight were present in 10/19 and cachexia in 3/18 of cases. 3/18 of patients, all with lymphocytic hypophysitis, had significantly elevated systolic and diastolic blood pressure. Lipid disturbances were diagnosed in 12/19 of patients (among them in 7/11 of relatively young patients with congenital malformations, in 9/12 of patients with secondary hypothyroidism and in 10/15 of cases with somatotropic axis deficiency). 3/19 patients characterized with higher values of liver enzymes (ALT, AST, GGTP). Vitamin D deficit was found in 10/19 of cases. Hyperinsulinemia/insulin resistance were found in 6/19 of patients (only 2 of them were on hydrocortisone).
Conclusions
The diagnosis, management and treatment of the pituitary stalk lesions remain challenging. Difficulties in establishing the exact diagnosis mightbe related to the non-specific, transient characteristics of the symptoms and hormonal insufficiencies. Metabolic abnormalities in patients with hypopituitarism caused by PSL are very common. Long term observations might help better the understanding of the disease and result in improvement of management.

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AEP746

Preoperative pegvisomant as a potential therapeutic option to improve cardiac function in Acromegaly-induced cardiomyopathy: Two cases

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Introduction
Acromegaly is a rare chronic disorder caused by growth hormone hypersecretion due to GH-producing pituitary adenoma. Surgery is the first-line treatment modality. However, patients with severe cardiac involvement are high-risk candidates for pituitary surgery. These patients may benefit from rapid preoperative biochemical control of acromegaly. There is emerging evidence of efficacy of pegvisomant, a GH-receptor antagonist, (either alone or in combination with somatostatin receptor ligands) in achieving rapid normalization of IGF-1. However clinical experience in using pegvisomant as monotherapy in preoperative setting in high-risk cardiac patients is lacking. We present two cases with acromegaly-induced dilated cardiomyopathy (DCM) who had preoperative treatment with pegvisomant.
Case reports
Case 1: A 53-year-old woman with biochemically confirmed acromegaly (random GH 10.5 mg/l (normal range 0.02–1.23), IGF1 1015 mg/l (normal range 71–224)) was referred to our clinic. Neuroimaging (MRI) of the head revealed a pituitary adenoma (15×14×6 mm). The patient was considered high-risk for surgery due to acromegaly-induced comorbidities especially the heart failure with reduced left ventricular ejection fracture (LVEF) of 29% and a severe mitral insufficiency. In addition, she had diabetes and obstructive sleep apnea. We started treatment with pegvisomant (daly 10 mg). Within two months of treatment, the IGF-1 decreased to 450 mg/l. LVEF improved to 37%. Not surprisingly, diabetes control also got better with reduced requirement for insulin. Tongue size and upper airway swelling decreased as well. Resection of pituitary adenoma was uneventful with complete biochemical and structural remission. *Case 2*: A 46-year-old man was admitted with congestive heart failure. Imaging (TTE, cardiac MRI) revealed a DCM with a LVEF of 20% and a severe aortic regurgitation. Careful clinical examination revealed typical clinical findings suggestive of acromegaly. The diagnosis was confirmed by elevated random GH; 38 mg/l and elevated IGF-1; 1080 mg/l. MRI scan of the brain showed a pituitary adenoma with infiltration of the cavernous sinus (32×22×20 mm). To optimize cardiac function, aortic valve replacement was scheduled before pituitary surgery. In addition, we started preoperative treatment with pegvisomant. After two months, the IGF-1 decreased to 700 mg/l. The aortic valve replacement was successful. LVEF in this case remained unchanged in short-term follow-up. However, NT-proBNP was regredient. The pituitary surgery is still pending.
Discussion
Severe cardiovascular disease in patients with acromegaly portends high mortality rate (almost 100% within 15 years). Preoperative treatment with pegvisomant may reduce perioperative risk by rapidly normalizing IGF-1 levels.

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AEP747

A prospective, non-interventional, observational, multi-center study of quality of life in people with acromegaly receiving lanreotide autogel

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Background
Patients with acromegaly have substantially reduced quality of life (QoL). Delayed diagnosis is common and a long duration of untreated acromegaly leads to decreased QoL and increased morbidity and mortality.
Aim
This longitudinal study examined QoL in patients with acromegaly who received lanreotide autogel.
Material and methods
This was a 2-year prospective, observational, multicenter study conducted in Poland (NCT02396966). We included patients with acromegaly who received treatment with lanreotide autogel 120 mg for ≥3 months and <3 years. QoL was measured with the Acromegaly Quality of Life questionnaire (AcroQoL).
Results
Of 152 patients enrolled from November 2014 to May 2018 in 37 centers, 24 were excluded due to major protocol deviations; thus, results are reported for 128 patients in the study population. At baseline, the median (95% CI) time from diagnosis was 3.3 (2.8, 4.2) years, and the median (95% CI) time since lanreotide autogel initiation was 13.4 (10; 17) months. In 85.9% patients, acromegaly was symptomatic at baseline; headaches (57.0%), sweating (57.8%), and joint symptoms (64.1%) were most common. Hormonal and symptomatic control was stable from baseline to study completion. At baseline, treatment satisfaction was high (88.3% completely or rather satisfied). During the study, treatment satisfaction was unchanged for 88.2% of patients. Mean (95% CI) AcroQoL scores at baseline were as follows: total score, 50.3 (47.3, 53.3); physical dimension, 48.8 (45.2, 52.4); psychological dimension, 51.3 (48.2, 54.4); appearance subdimension, 40.7 (37.5, 43.8); and personal relations subdimension, 62.5 (58.8, 66.2). From baseline to month 24, the appearance subdimension improved 3.8 points (1.1, 6.4),

whereas the remaining AcroQoL scores did not change substantially. The total AcroQoL score remained unchanged over 2 years regardless of prior acromegaly treatment, prior surgery, prior radiotherapy, biochemical control, or lanreotide dosing interval. No new safety findings were identified.
Conclusions
Overall, global QoL and its physical and psychological aspects remained stable albeit compromised despite hormonal and symptomatic control throughout the study, whereas the AcroQoL psychological appearance subdimension improved. Most subjects remained satisfied with treatment during the study.
Keywords: acromegaly, somatostatin analogue, lanreotide, quality of life, AcroQoL

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AEP748

Soluble klotho: A possible predictor of quality of life in acromegaly patients

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Purpose
Although quality of life (QoL) is improved in patients with acromegaly after disease control, QoL correlates only weakly with traditional biomarkers. Our objective is to investigate a potential relation between the new serum biomarker soluble Klotho (sKlotho), GH and insulin-like growth factor 1 (IGF-1) levels and QoL.
Methods
In this prospective cohort study, we investigated 54 acromegaly patients biochemically well-controlled on combination treatment with first-generation somatostatin receptor ligands (SRLs) and pegvisomant (PEGV) at baseline and nine months after switching to pasireotide LAR (PAS-LAR; either as monotherapy, $n=28$; or in combination with PEGV, $n=26$). QoL was measured by the Patient-Assessed Acromegaly Symptom Questionnaire (PASQ) and Acromegaly Quality of Life (AcroQoL) questionnaire.
Results
Switching to PAS-LAR treatment significantly improved QoL without altering IGF-1 levels. QoL did not correlate with GH or IGF-1 levels, but sKlotho correlated with the observed improvements in QoL by the AcroQoL global ($r=-0.35$, $P=0.012$) and physical sub-dimension ($r=-0.34$, $P=0.017$), and with PASQ headache ($r=0.28$, $P=0.048$), osteoarthralgia ($r=0.46$, $P=0.00080$) and soft tissue swelling score ($r=0.29$, $P=0.041$). Parallel changes in serum sKlotho and IGF-1 ($r=0.31$, $P=0.023$) suggest sKlotho and IGF-1 to be similarly dependent on GH. Comparing the PAS-LAR combination therapy and the monotherapy group we did not observe a significant difference in improvement of QoL.
Conclusion
Patients experienced improved QoL during PAS-LAR, either as monotherapy or in combination with PEGV. Soluble Klotho concentrations appear to be a useful marker of QoL in acromegaly patients but the underlying mechanisms remain to be investigated.

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AEP749

Pregnancy outcomes in women receiving growth hormone therapy enrolled in NordiNet international outcome study (IOS) and American Norditropin Studies: Web Enabled Research (ANSWER Program)

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Recombinant human growth hormone (GH) is not indicated for use during pregnancy and in women of childbearing potential not using contraception. Nonetheless, in clinical practice, some women taking GH replacement conceive during treatment and many continue GH during their pregnancy. Here we report data on GH-treated women enrolled in two complementary, international, non-interventional registry studies, NordiNet IOS (NCT00960128; 2006–2016) and ANSWER (NCT01009905; 2002–2016), that assessed effectiveness and safety of real-life treatment with Norditropin (somatropin). Patient information was entered at routine clinic visits by participating physicians using a web-based system. Overall, 54 pregnancies were reported in 40 female patients with GH deficiency (GHD): 28 women had one pregnancy, 10 had two and two had three pregnancies. Median (range) age at estimated conception date was 31.9 (23.0–41.8) years. Pituitary disease aetiology included pituitary/hypothalamic tumours/adenomas in 27.5%, craniopharyngioma in 12.5%, idiopathic/congenital in 25.0% and other causes of acquired GHD in 30.0%. Seven patients had isolated GHD. Twenty-four (60.0%) patients had adult-onset GHD and 14 (35.0%) had childhood-onset GHD (missing, $n=2$). At baseline, 27.5% of patients reported one additional pituitary hormone deficiency, 10.0% had two, 17.5% had three, 20.0% had four, 2.5% had five and 5.0% had six. Deficiency of LH/FSH was present in 50.0%, TSH in 42.5%, ACTH in 35.0% and ADH in 12.5% of patients at conception. Seven (17.5%) patients had diabetes insipidus. GH dose (mg/day) at conception was >0.6 in 20 (37.0%) pregnancies, 0.4–0.6 in nine (16.7%) and ≤0.4 in six (11.1%). In seven (13.0%) pregnancies GH therapy was stopped by conception, permanently discontinued/stopped before study inclusion in two (3.7%), and patient was not treated in two (3.7%) (missing, $n=8$). During pregnancy, GH therapy was stopped (≤5 months/before conception) in 27 (50.0%) pregnancies, partially continued (> 5 –<7 months) in two (3.7%) and continued in 16 (29.6%) pregnancies (no treatment, $n=3$; missing, $n=9$). Among the 18 pregnancies with continued/partially-continued GH therapy, mean daily dose was >0.6 mg in 10, 0.4–0.6 mg in six and ≤0.4 in two. Forty-two (77.8%) pregnancies resulted in the birth of a healthy child; no birth defects were reported. There were five (9.3%) spontaneous abortions and two elective terminations (patient wish, $n=1$; medical indication, $n=1$). Outcome was unknown for five pregnancies.
In these women, most pregnancies resulted in the birth of healthy children. These data add to available knowledge on the outcome of pregnancy in GH-treated women with GHD.

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AEP750

Country-specific differences in adult growth hormone deficiency diagnosis and treatment rates

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Background
Adult growth hormone deficiency (AGHD) is a rare disease associated with adverse metabolic abnormalities and possibly increased cardiovascular morbidity and mortality. Although basic prevalence data is available, little is known about the rates of diagnosed and treated patients.
Aim
To understand the rates of AGHD diagnosis/treatment and details about patients' growth hormone (GH) dose, age and treatment duration.
Methods
From 2015–2018, 435 endocrinologists across US, Germany, Switzerland, UK, France and Japan completed a survey providing details about the number of AGHD patients under their care, number of patients treated, GH dose, age and treatment duration. Percentages of undiagnosed patients were estimated based on respondents' projections of undiagnosed patients and published prevalence literature. Results were stratified by country and AGHD subtype (childhood onset [CO], pituitary adenoma [PA] and traumatic brain injury [TBI] and others [not shown]).
Results
The numbers of diagnosed and GH-treated adult patients across the six countries are shown in Table 1. In the US, Germany, Switzerland and UK, mean GH dose ranged from 0.43–0.78, 0.42–0.48 and 0.40–0.56 mg/day for AGHD-CO, -PA and -TBI, respectively. The opinion of the respondents regarding the gap in diagnosis is summarised in Table 2. Treatment duration, drop-out and resumption rates varied by country and AGHD subtype.

Table 1

	US	Germany	Switzerland	UK	France	Japan
AGHD-CO						
Patients diagnosed, N	3,325	1,252	142	2,052	560	1,346
Patients treated, N (%)*	2,333 (70.2)	964 (77.0)	101 (71.1)	1,549 (75.4)	438 (78.2)	1,070 (79.5)
AGHD-PA						
Patients diagnosed, N (%)	7,177	2,059	211	5,215	1,658	2,323
Patients treated, N (%)*	3,352 (46.7)	1,128 (54.8)	119 (56.3)	3,695 (70.8)	1,283 (77.4)	1,751 (75.4)
AGHD-TBI†						
Patients diagnosed, N (%)	6,324	1,651	123	1,735	553	1,093
Patients treated, N (%)*	2,229 (35.2)	768 (46.5)	61 (49.6)	1,255 (72.3)	428 (77.4)	824 (75.4)

*Of diagnosed patients. †AGHD-TBI with persistent hypopituitarism.

Table 2

	US	Germany	Switzerland	UK	France	Japan
Estimated undiagnosed patients,%						
AGHD-CO	17.4	16.1	15.1	34.0	18.6	4.7
AGHD-PA	56.4	53.2	53.7	31.0	21.3	36.0
AGHD-TBI*	64.3	54.7	55.7	42.0	21.3	35.8

*AGHD-TBI with persistent hypopituitarism.

Discussion
The analysis suggested substantial differences in diagnosis/treatment rates of AGHD-PA and AGHD-TBI, with lower rates in US, Germany and Switzerland compared with UK, France and Japan. The AGHD-CO diagnosis/treatment rates were relatively high everywhere as expected based on preceding childhood diagnosis. Determining the causative factors behind country-specific differences in GH treatment may help improve care for AGHD patients.

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AEP751

Evaluation of haemolitic complement activity (ch50) and igg subclasses in adult growth hormone deficiency: Preliminary data

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Adult Growth Hormone Deficiency (GHD) is a condition characterized by low grade chronic inflammation; increased levels of free light chains of immunoglobulins have been described; moreover, it shares some features with metabolic syndrome (MetS), including insulin resistance and oxidative stress, but with a different pattern of antioxidant response. Finally, it is known that GH, directly or via IGF-1 activity, influences many aspects of immune response; both humoral and cellular branches are modulated, but no data are available about complement function.
CH50 is a screening assay for the activation of the classical complement pathway and it is sensitive to the reduction, absence and/or inactivity of any component of the pathway. The CH50 tests the functional capability of serum complement components of the classical pathway to lyse sheep red blood cells (SRBC) pre-coated with rabbit anti-sheep red blood cell antibody (haemolysin). The subclasses of IgG can also depict a scenario of immune response, knowing the different functions of specific subclasses. No data are reported on CH50 and IgG subclasses in GHD.
Therefore, we performed a case-control study in a group of adult GHD patients evaluating CH50 levels and IgG subclasses to further explore the pattern of inflammatory markers in this condition.
We includedpatients with total GHD (GH peak after stimulation with GHRH+arginine <9 ng/ml with BMI < 30 or <4 ng/ml with BMI ≥ 30 kg/m^2; $n=15$) or partial GHD (peak between 9 and 16 ng/ml with BMI < 30 kg/m^2 $n=12$) with mean ± SEM BMI 27.7 ± 2.6 kg/m^2 and mean ± SEM age 51.3 ± 2.5 ys. We also included a control group ($n=29$) of patients matched by age (mean ± SEM 49.4 ± 1.7 ys).
An opposite pattern of the parameters studied was observed, with a significant increase of CH50 in GHD vs controls (Mean ± SEM 51.2 ± 2.5 and 30.5 ± 1.7 U/l respectively, $P<0.05$), while a significant decrease of IgG4 was present in the same groups (0.23 ± 0.05 and 0.62 ± 0.11 g/l respectively, $P<0.05$).
These datasubstantiate the hypothesis of chronic low-grade inflammation in GHD even if a causal relationship cannot be established and a vicious circle could ensue, with increase in inflammatory molecules in turn influencing GH secretion. However, these data cannot be conclusive and further studies are needed to establish the role of such molecules as biological markers and their usefulness in prognostic and personalized treatment of such condition.

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AEP752

FDG PET contribution to ectopic prolactinoma diagnosis - case report

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Pituitary adenomas are in the majority of cases diagnosed by magnetic resonance imaging (MRI). In some cases, especially in functional tumors, there are too small adenomas for MRI resolution and we need other diagnostic modality (including petrosal sinus catheterization for laterality). Usefulness of positron emission tomography (PET) with fluorodeoxyglucose was demonstrated in some case report. In this case, we present 36 y/o women with no other comorbidities, which came at first in 2012 for 10 months persistent amenorrhea with normal gynecologic finding. Diagnosis of hyperprolactinemia was determined (PRL 2820 mIU/l = 132.5 ng/ml; 7 × ULN) and treatment with cabergoline (0.5 mg/weekly) was started. MRI revealed 4 mm microadenoma in right half of pituitary gland. Other pituitary function were normal. Until 6 months, PRL was normalized and cycle was restored. Next follow-up was lost. After five years, the patient came with the same problem – persistent amenorrhea with minor PRL elevation (1398 mIU/l), we started the same treatment with cabergoline. In contrary to previous course, no effect was observed, PRL increased regardless of the cabergoline dose (max 2 mg daily). Other pituitary functions remained normal. Switch to bromocriptine and next to quinagolide was not successful, maximal tolerated doses were completely inefficient and PRL was continuously increased (to 7038 mIU/l). MRI repeatedly (altogether 3 examinations in 1.5 year) with no pituitary pathology, originally founded microadenoma in right half of pituitary gland was disappeared. Macroprolactinemia was excluded. Therefore PET/MRI with FDG was performed, even with thought of ectopic prolactinoma. Surprisingly, we found thin (3 mm) strip of tissue around left carotid artery with sphenoid propagation (length 10 mm), with increased FDG uptake (SUV max 15). No other pathology was found. Neurosurgery cannot be radical in this case and then this locus was irradiated by gamma knife (35Gy on 46% isodose, Dmax 76Gy) with decreased PRL level to 1041 mIU/l after 3 months and 890 mIU/l after 6 months. MRI after 6 months showed regression of this "ectopic" prolactinoma to 4.5 mm length.
Conclusion
Treatment resistant hyperprolactinemia represents less than 5% of prolactinomas. Irradiation or neurosurgery are possible therapeutic modalities.

Hybrid radiologic methods (PET FDG with MRI) can contribute to diagnosis in cases of ectopic or very small pituitary tumors.

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AEP753

SF-12 or SF-36 in pituitary disease? towards concise patient-reported outcomes measurements

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Objective
Pituitary diseases cause a wide range of local and systemic symptoms and severely affect patients' health-related quality of life (HRQoL), which can be monitored using both disease-specific and generic questionnaires. The most frequently used generic HRQoL questionnaire is the Short Form-36 (SF-36), generating a mental (MCS) and physical component score (PCS). The shorter 12-item version (SF-12) can improve efficiency of patient monitoring and outcome measurement and reduce the burden for patients. This study therefore aimed to determine whether the SF-12 can be used instead of the SF-36 in pituitary care.
Study design and methods
Data of a longitudinal perioperative cohort study (August 2016 – December 2018) were used, comprising 103 adult patients endoscopically operated for a pituitary adenoma with 6 months follow-up. A chronic care cross-sectional cohort study in 431 adults with a pituitary tumor was analyzed in parallel. Both studies were conducted in a tertiary referral center in the Netherlands. The PCS and MCS of SF-36 and SF-12 were measured preoperatively, and 6 weeks and 6 months postoperatively. Agreement between questionnaires on each timepoint and over time was assessed with intraclass correlation coefficients (ICC) and Bland-Altman plots, presenting the limits of agreement (95% of the observed values). Linear regression analysis was used to determine the association of baseline factors with a large individual difference (>5 points) between SF-36 and SF-12.
Results
For PCS, ICCs were 0.590 preoperatively, 0.548 at 6 weeks and 0.622 at 6 months. ICCs for MCS were higher, respectively 0.952, 0.948, and 0.943. At the same time points, mean differences between SF-36 and SF-12 were 4.1, 4.7 and 5.9 points for PCS, and 1.3, 1.5, and 1.7 points for MCS. Limits of agreement for change (6 months vs preoperatively) were –14.0 to 16.9 for PCS and -7.8 to 8.7 for MCS. Similar results were found in the cross-sectional cohort. No baseline factors were consistently associated with a large individual difference between the SF-36 and SF-12.
Conclusions
The SF-12 can reliably reproduce the MCS in pituitary patients, but PCS of SF-36 and SF-12 is less well correlated. Moreover, wide limits of agreement show that individual differences between the SF-36 and SF-12 can be large. The SF-36, that also offers the advantage of generating HRQoL domain scores, is therefore recommended for use in pituitary care. Further strategies to reduce the number of questions in both validated generic and disease-specific HRQoL questionnaires must be evaluated for this patient population.

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AEP754

The role of surgery in the treatment of craniopharyngioma: A comparison of the transsphenoidal approach and the interbasal hemisphere approach based on surgical outcomes

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The transsphenoidal approach has been utilized in intrasellar craniopharyngioma surgeries. However, the advent of endoscopic extended transsphenoidal approach (EETSA) has expanded its indication to suprasellar craniopharyngiomas. We compared the indication and limitations of EETSA to those of unilateral basal interhemispheric approach (UBIHA), which presents similar indications for surgery. We analyzed 60 patients with tumors located below the foramen of Monro and the lateral boundary extending slightly beyond the internal carotid artery (UBIHA: $n=36$; EETSA: $n=24$). Postoperative magnetic resonance imaging (MRI) revealed gross total resection in 20 patients in the EETSA group (83.3%) and 24 in the UBIHA group (66.7%). Postoperative MRI in the EETSA group revealed residual tumor at the cavernous sinus in two patient, at the prepontine in two; in the UBIHA group, residual tumors were located in the retrochiasmatic area in four patients, infundibulum-hypothalamus in two, on the stalk in two, and in the intrasellar region in two. No intergroup differences were observed in the preservation of pituitary function and postoperative improvement of visual function. The extent of resection was better with EETSA than with UBIHA. EETSA is considered the first-line therapy because the distance between the optic chiasm and the superior border of the pituitary is large; the lateral extension does not go beyond the internal carotid artery; and the tumor does not extend inferiorly beyond the posterior clinoid process. However, in patients showing poorly developed sphenoid sinuses or pituitary stalks anterior to the tumor, surgery is difficult regardless of the selection criteria.

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AEP755

An analysis of incidence and characteristics of cushing's syndrome in malta: A population based study

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Aim
There are few reports discussing incidence and characteristics of the whole group of Cushing's syndrome patients in the literature. The aim was to establish the incidence of endogenous Cushing's syndrome with in-depth analysis of their various subtypes in a well-defined population.
Methods
Retrospective cross-sectional analysis of Cushing's syndrome patients diagnosed between 2008 and 2017. A thorough search for patients was carried out in the central hospital registries including outpatients departments, surgical registries, radiological department and specialty clinic databases.
Results
26 patients were identified as diagnosed with Cushing's syndrome over the 10-year period equating to a standardised incidence rate (SIR) of 4.7/1,000,000/yr with an almost equal SIR among males and females. Analysing the various subtypes of Cushing's syndrome, the majority ($n=13$) were due to an ACTH secreting pituitary adenoma (SIR 2.5/1,000,000/yr). In this subtype males had a SIR of 3.4/1,000,000/yr compared to 1.7/1,000,000/yr in females. ACTH independent Cushing's had a SIR of 1.8/1,000,000/yr with a strong female predominance (9:1) (SIR females: 3.0/1,000,000/yr; males: 0.5/1,000,000/yr). The SIR of ectopic ACTH secreting tumours was 0.4/1,000,000/yr. Interestingly hypokalaemia was present at diagnosis in those patients who harboured malignant causes for their Cushing's syndrome (ectopic ACTH secreting tumours or adrenocortical carcinomas) and had markedly elevated cortisol levels at baseline compared to the rest ($P<0.001$). Mean cortisol post overnight dexamethasone suppression test-was 1714 nmol/l (± 692 S.D.) in the malignant patients and 522 nmol/l (± 288 s.d.) in those patients with a benign tumour ($P=0.004$). Mean ACTH values for Cushing's disease patients was 110.4 (± 77.2 SD) pg/ml while in the ACTH independent group it was 5.5 (± 4.7 S.D.) pg/ml ($P<0.001$).
Conclusion
Cushing's syndrome is a rare disease. Although the numbers are small, we could still establish distinct characteristics in the different subtypes.

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AEP756

Patients receiving a range of doses of prior injectable somatostatin receptor ligands respond to oral octreotide in the treatment of acromegaly: Results from the phase 3 optimal study

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Background
Injectable somatostatin receptor ligands (SRLs) are the most widely used therapy to control acromegaly. Oral octreotide capsules (OOC) have been formulated as a potential therapy for this disorder and the efficacy and safety was evaluated in the CHIASMA OPTIMAL prospective phase 3 study in patients with acromegaly who were controlled on injectable SRL treatment of varying doses (Samson *et al*. ENDO 2020).
Methods
Patients with confirmed acromegaly who had been receiving a stable dose of injectable SRL (≥3 months), were randomized to receive OOC (40 mg/day) or placebo for 36 weeks. Patients were dose titrated to 60 or 80 mg OOC or equivalent placebo through week 24 at the investigator's discretion based on increased IGF-I levels or worsening acromegaly signs/symptoms. The primary efficacy endpoint was the proportion of patients who maintained their biochemical response at the end of 36 weeks, defined as average IGF-I ≤1 xULN between Weeks 34 and 36. An analysis evaluated maintenance of response based on prior dose of injectable SRL. Prior doses of injectable SRL were categorized based on the following classifications: octreotide 10 mg every 4 weeks or lanreotide 60 mg every 4 weeks or 120 mg every 8 weeks were stratified as low; octreotide 20 mg every 4 weeks or lanreotide 90 mg every 4 weeks or 120 mg every 6 weeks were stratified as medium; octreotide 30 mg or 40 mg or lanreotide 120 mg every 4 weeks were stratified as high. Randomization was stratified based on low dose vs med/high dose and efficacy results compared for these strata. The response rates reported for the primary endpoint are adjusted for stratification differences as prespecified in the statistical analysis plan.
Results
Six patients (21.4%) in the OOC group had received prior treatment with low doses of injectable SRLs while 22 (78.6%) had received prior treatment with medium-high doses of injectable SRLs. Maintenance of response was observed in 16 patients receiving OOC. This included 66.7% of patients (n=4) previously receiving low doses of injected SRLs and 54.5% of patients (n=12) on medium-high injected doses. The treatment effect was consistent irrespective of prior dose of injectable SRL (odds ratio: 5.4 in low dose and 5.9 in medium-high dose).
Conclusion
The CHIASMA OPTIMAL study recruited a population receiving predominantly medium-high doses of injectable SRLs and demonstrated maintenance of response in 58% of patients. OOC treatment effect was consistent irrespective of prior dose of injectable SRL.

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AEP757

AIP gene germline mutations in non-selected patients with sporadic pituitary macrodenomas

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Up to 5% of all pituitary tumors are hereditary (e.g. due to menin or AIP genes mutations). AIP gene mutations are more common in subjects with acromegaly, less than 30 years old at the onset of disease, and with FIPA family history. The study was aimed at the assessment of the frequency and characteristics of AIP-mutation related tumors in non-selected patients with pituitary macroadenomas.
Material and methods
The study included subsequent 131 patients (57 males, 74 females; median age 42 years (IQR 25 years) diagnosed with pituitary macroadenomas, and with a negative family history of FIPA or MEN1 syndromes. The following tumors were identified: 11 ACTH-secreting, 49 GH-secreting (including 7 pluri-hormonal ones), 6 gonadotropinomas, 23 prolactinomas, 1 TSH-oma, and 43 non-secreting adenomas. Sanger sequencing was used for the assessment of AIP gene variants. The study was approved by the Ethics Board of JUMC.
Results
An AIP mutation was identified in five of 131 included subjects (3.8%): one diagnosed with Cushing's disease, two with acromegaly, and two with non-secreting adenomas. In two patients, the identified mutation usually predisposes to ACTH-secreting adenomas, in two patients – mutations of unknown clinical significance were found (usually connected with pituitary adenomas), and the mutation detected in one patient was described as benign. Patients harboring hereditary AIP gene variations did not differ from the rest of the study group in median age at diagnosis (41 vs 42.5 years, P=0.8), median largest tumor diameter (25 vs 24 mm, P=0.6), gender distribution (60% of females vs 56.3%, P=0.8), secreting tumor frequency (60% vs 67.5%, P=0.7), or acromegaly diagnosis frequency (40% vs 37.3%, P=0.9). 2 of the 5 patients with identified AIP gene mutations agreed for their families to be offered AIP genetic testing: (1) An AIP mutation was found in the asymptomatic mother of one acromegalic female patient. (2) The AIP mutation of unknown clinical significance was detected in the son of a male patient with acromegaly, clinically unscreened yet.
Conclusions
In our series of apparently sporadic pituitary macroadenomas, AIP gene mutation carriers did not differ substantially from patients with negative genetic testing. A risk factor-centered approach to AIP genetic screening may result in missing germline mutations, therefore, there is a need to establish if such a situation negatively impacts a patient's and his/her family outcomes.

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AEP758

Silent corticotroph adenoma: Experience with six cases

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Introduction
Silent corticotroph adenomas (SCA) represent a subtype of pituitary adenomas whose prevalence is 3% of pituitary adenomas. They are characterized by having a positive immunohistochemistry to corticotropin (ACTH) without clinical or biochemical data of hypercortisolism. The diagnosis is a challenge since they are considered as ANF, and it is with the pathology report after surgery when they are classified as SCA. They have more aggressive behavior and recur more than ANF
Case Report
Of the 129 pituitary adenomas operated on in our hospital in the last ten years (2009 – 2019), six SCA were found. The average age was 58.8 years (45 – 72) and 4/6 cases (67%) were women. All were macroadenomas, with an average size of 27 mm±8, with headaches in 5/6 (83%) and visual disturbances in 5/6 (83%). None of them showed signs and/or symptoms of hypercortisolism. Type 1 SCA was found in 3/6 (50%) and type 2 in the other 50%. The average preoperative ACTH value was 59 pg/ml±29, with an average cortisol of 13 µg/dl±2. Four out of six cases (67%) had high ACTH levels and all had normal plasma cortisol. Five of six cases (83%) had invasion of cavernous sinus and 2/6 (33%) suffered an apoplexy. Knosp's grade of cavernous sinus invasion was equal to or greater than 3 in 4/6 cases (67%). Multiple microcysts were found in the T2 sequence of pituitary MRI in 5/6 cases (83%), a liquid content of less than 50% in 4/6 (67%) and more than 50% in 2/6. Five of six cases (83%) presented with preoperative hypogonadotropic hypogonadism. Two of six cases (33%) presented "de novo" postoperative hypopituitarism. The average follow-up time was 37 months (3–78). Of six cases, two experienced a progression after surgery, one had a stable remnant, two did not have a remnant and one waiting for the pituitary MRI. The two cases that progressed had highervalues of ACTH, Knosp's grade and Ki-67, with less than 50% liquid content. Both required radiotherapy and one of them a second surgery
Conclusions
- SCA are a subtype of pituitary adenomas whose diagnosis regarding ANF is difficult. A high preoperative ACTH value and/or the presence of multiple microcysts in the T2 sequence of pituitary MRI could make us suspect the existence of SCA
- Because of the greater recurrence, SCA require closer clinical and radiological follow-up and an evaluation by a multidisciplinary team

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AEP759

MRI follow-up of patients with acromegaly treated with first-generation somatostatin analogues (SMSa): Is there a difference during primary or post-operative treatment?

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Objectives
First-generation SMSa are the medical treatment of choice in the management of acromegaly, mainly as adjuvant treatment of pituitary surgery when normal IGF-1 is not obtained or as primary treatment in selected patients. The main objective of this study is to evaluate regular pituitary MRI follow-up of acromegalic patients treated with SMSa as adjuvant treatment of pituitary surgery. The secondary objective is to compare the anti-tumoral effect of SMSa in post-operative period to the effect observed during primary treatment of acromegalic patients.
Patients and methods
In a monocentric, retrospective study we included all acromegalic patients treated with SMSa after a pituitary surgery or first-line therapy, and regularly followed by MRI scans for at least 3 years. The height of pituitary adenomas or post-operative remnants was measured along the coronal plane, perpendicularly to the optic chiasm, and all MRI scans are seen by the same neuro-radiologist.
Results
We included 27 patients (11 women, 16 men, mean age 39.5±12.2 years) treated with SMS a after surgery. The post-operative evaluation revealed persistent GH/IGF-1 hypersecretion (GH=4.2±9.9 ng/ml, IGF-1=175±74% ULN) and adenoma remnants (9.25±5.34 mm). After 6.1±4.5 years of SMSa treatment,the adenoma height did not decrease significantly in controlled (n=11, 8±5.0 vs 6.5±3.5mm, ns) or uncontrolled (n=16, 9.78±5.54 vs 9.35±4.71mm, ns) patients, with 20 adenoma remnants remaining stable. A significant increase (≥ 2 mm) of adenoma height was observed in a patient with acromegaly revealed by pituitary apoplexy and with histological aggressiveness criteria. Eighty three patients (32 men, 51 women, mean age 50±12 years) with mean GH=19.3±25.6 ng/ml, IGF-1=284±110 % ULN and pituitary adenoma height=12.9±4.7 mm were primary treated with SMSa : adenoma height decreased significantly in controlled patients (11.9±4.8 mm vs 9.6±3.3 mm, P<0.001) after 8.9±4.9 years, and in partially responders (13.6±4.5 mm vs 11.5±4.5 mm, P<0.001) after 2.0±1.6 years. Compared to the patients post-operative treated with SMSa, a greater anti-tumor effect was observed when SMSa was primary administered (2.20±3.03 mm vs 0.75±2.65 mm, P<0.02).
Conclusion
This clinical study shows that regular post-operative MRI monitoring of adenoma remnants does not seem necessary during SMSa treatment, but it remains indicated for rare patients with atypical adenoma and histological aggressiveness criteria, and confirms that first-generation SMS a have an anti-tumoral effect significantly lower in adjuvant treatment than in primary treatment.

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AEP760

Associations of endocrine and metabolic complications of childhood- and adult-onset craniopharingeoma with the histological subtype

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Objective
Studies comparing endocrine and metabolic outcomes of childhood- and adult-onset craniopharyngioma (CP) are generally based on the age-of-disease onset only. The aim of this study was to analyze the role of histological tumor subtype (adamantinomatous (aCP) or papillary (pCP)) on the development of long-term endocrine and metabolic CP comorbidities.
Methods
47 patients with CP treated from 1979 onwards (19 patients with childhood-onset disease) in a single center university institution were included. Median follow-up since presentation was 13 years (interquartile range: 0.2 – 38 years) and comparable between age-of-disease-onset and histological subtype groups. Data on tumor histology was extracted from patients' records, and re-evaluated by a single by an experienced pathologist when tissue samples were still available.
Results
At presentation 54% of childhood- and 41% of adult-onset CP patients had at least one pituitary axis affected. Individual hormonal axis were similarly affected when groups were compared by age-of-diagnosis or histology subtype. At follow-up 100% of childhood- and 93% of adult-onset patients had at least one pituitary hormone deficiency. Growth hormone (GH) deficiency, central diabetes insipidus and panhipopituitarism were more prevalent in childhood-onset aCP and least prevalent in adult-onset pCP. 20% of childhood-onset CP patients were already obese at diagnosis, whereas none of the adult-onset patients were obese. At follow-up only 11% of patients with childhood- and 4% of adult-onset CP were normal weight, with obesity rate increasing to 55% in the first and 46% in the latter group. Risk for obesity positively correlated with the presence of hydrocephalus at diagnosis, hypothalamic and third ventricular floor damage after surgery. Metabolic syndrome (MetS) was present in 80% of childhood- and 68% of adult-onset patients.
Conclusions
Long-term endocrine and metabolic complications are very frequent in CP patients. Patients with a CP, especially with childhood-onset, are generally more affected.

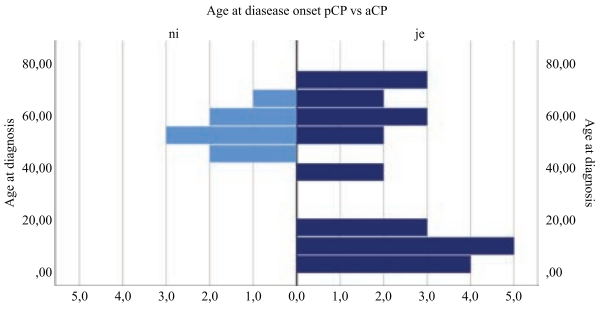

Figure 1 Frequency of CP diagnosis according to age-of-diagnosis and histological subtype.
Light blue – pCP
Dark blue – aCP
Data on histological type was missing in 6 childhood-onset CP and 7 adult-onset CP.

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AEP761

The united russian registry on patients with acromegaly

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Background
The registry is the main source of information about patients with acromegaly for assessing the quality of medical care, effectiveness of treatment, determining the compliance of real clinical practice with existing standards and patient management protocols.
Aims
To analyze the epidemiological, demographic and clinical characteristics of acromegaly in the Russian Federation and the effectiveness of various treatment methods.
Materials and methods
The object of the study was the database of the united Russian registry of patients with pituitary tumors with specific analysis of patients with acro-

megaly only. We analyzed 4114 patients with acromegaly included in the online system by February 2019.
Results
Based on the data collected by February 2019 32% of patients had complete clinical and laboratory remission of the disease; the percentage of patients with no remission was 68%, among them 22.5% had significant improvements in clinical presentations and decrease in GH and IGF1 without IGF1 normalization. The average age of patients at the onset of the disease was 42.7 years, at the stage of diagnosis – 45.8 years. The ratio of men to women was 1:2.6.Among patients with acromegaly and hypopituitarism complications such as hypothyroidism (66%) and hypogonadism (52%) were registered more often followed by secondary diabetes mellitus (15.7%) and acromegalic arthropathy (15%). The proportion of patients receiving neurosurgical treatment increased from 35.7% to 49.6% in 2012 – 2019; the percentage of patients undergoing radiation therapy decreased significantly from 17.7% in 2012 to 0.8% in 2019. Remission was achieved in 40.47% after neurosurgery and 28.95% after medical treatment as a first line therapy $P<0.01$. The number of patients receiving medical treatment at the time of the study was 1209. Among them 51% of patients being treated with long-acting lanreotide and 24% receiving long-acting octreotide achieved remission ($P<0.0001$)
Conclusions
Remission of acromegaly remains suboptimal despite increased surgical activity, which corresponds to global trends. Long-acting lanreotide was significantly superior versus long-acting octreotide in the rate of acromegaly remission, which does not correspond with clinical trials and can be explained by the generic forms, regional differences in medical supply and demand towards medical nurse qualification with regards to the injection of long-acting octreotide.

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AEP762

Immunohistochemical subtypes of growth hormone-secreted pituitary adenoma and relationship with the clinical course and seconder malignancy

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Purpose
Most of the acromegaly cases are due to agrowth hormone-secreting pituitary adenomas of which immunohistochemical subtype seperated as sparsely granulated adenoma (SGA) and densely granulated adenoma (DGA). SGA's were reported to have more aggressive clinical course and therapy resistance. We investigated our patients for these aspects.
Method
Forty (F21, M19) patients with acromegaly who diagnosed and operated for pituitary adenoma at our University Hospital were included. Medical history, duration of the disease and comorbidities were assessed. Considering the current guidelines for acromegaly managements, serum growth hormone (with 75 g oral glucose tolerance test-OGTT), insulin like growth factor 1 (IGF-1) levels, computed tomography (CT) or magnetic resonance imagings (MRI) of the pituitary were performed. Immunohistochemical staining of postoperative tissue materials and subtypes of pituitary adenomas were evaluated by an experienced cytopathologist.
Results
Mean age of the patients was 48 years (range, 30 – 66). Of 40 patients, 30 had macroadenoma and 10 microadenoma. There were 25 (25/40) patients with SGA and 15 (15/40) with DGA. The remission rate after primary surgery of 40 patients was 9/40. Of 9 patients, 2 were SGA (2/25) and 7 DGA (7/15) ($P=0.001$, SGA vs DGA). Complete disease remission was seen in 15 of 40 (37.5%) patients. In those who achieved endocrine remission, 9 had only transsphenoidal surgery (TSS) and the remaining 6 patients were treated with somatostatin analogues and gamma-knife radiotherapy additional to TSS. As compared with the DGA, SGA showed more cavernous sinus infiltrasion (18 vs 10, $P=0.05$). Abnormal abdomen ultrasonography findings including hepatomegaly, hepatosteatosis, splenomegaly were found in all patients with SGA, but only in 6 patients with DGA. Furthermore, 4 neoplasia of the other site of body were found in the patients with SGA.
Conclusion
Immunohistochemical subtype of the pituitary adenoma seemed to have potential to affect the clinical course and therapy of acromegaly. SGA was revealed as more prone to cavernous sinus invasion, comorbidity and resistance to therapy. Carcinogenesis related with malignancy was more common in patients with SGA. Further studies are needed.

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AEP763

Prolactinoma In childhood and adolescence – a systematic review and meta-analysis

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Background and Objective
Data on the epidemiology, effects of dopamine agonists and long term outcome of prolactinoma in children and adolescents have been gradually accumulating but are still scarce. We conducted a systematic review and meta-analysis of published literature (1994 – 2019) to study the epidemiology of prolactinoma in patients<20 years old, and determine the management strategies adopted.
Methods
Relevant studies were identified through Medline search and from the reference list of retrieved studies. Pertinent data were extracted. Both "random" and "fixed" effects meta-analysis were used to pool outcomes across studies.
Results
Of 635 articles retrieved, 610 were discarded during the title and abstract analysis. Another seven articles were excluded after full-text analysis as they did not report on our research questions. A total of 18 articles, describing 487 patients, were then reviewed. A pronounced sex difference was noted with 75.7% (95% CI 69.6 to 81.3%) of patients being female. Patients were divided into those with macroprolactinoma ($n=288$), microprolactinoma ($n=151$) and size not specified ($n=48$). After excluding one large series which reported only macroprolactinomas, the proportion of patients with macroprolactinomas (57.6% [95% CI 51.2% to 64.0%]) was still higher than with microprolactinomas. Both macroprolactinomas (134 vs 67 F:M) and microprolactinomas (137 vs 6 F:M) were more common in females as compared to males. Even more striking was the difference in the distribution of size (micro/macro) between the two sexes. In males, only 6/73 (8.2%) of tumours were microprolactinoma as compared to 137/271 (50.5%) in females (risk difference 0.463; [95% CI 0.386 to 0.541]; $P<0.001$). Medical or surgical therapy was adopted as first-line therapy in 67.4% and 32.6% respectively. Surgery was, surprisingly, the initial treatment in 87/273 (31.9%) with macroprolactinoma, and 26/126 (20.6%) with microprolactinoma. In patients where the initial treatment was medical, 45/186 (24.2%) of macroprolactinoma patients and 20/100 (20%) of microprolactinoma patients subsequently proceeded to surgical intervention. Growth hormone, Adrenocorticotrophic hormone, Thyrotropin and Arginine Vasopressin deficiency were reported in 39 (8.7%), 43 (9.6%), 47 (10.5%) and 15 (3.3%) patients respectively (inadequate data to qualify whether pre- vs post-surgery.
Conclusions
Microprolactinoma occurs almost exclusively in females and is an uncommon diagnosis in males in this age group. Macroprolactinoma is also more common in girls compared to boys. A surprising number of patients proceeded to surgery before medical therapy, and surgery is part of overall management in a substantial proportion. Association with other pituitary hormone deficienciesis not uncommon.

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AEP764

Combined pitutitary hormone deficiency in a patient with charge syndrome

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Background
CHARGE is an autosomal-dominant syndrome which includes a variable combination of ocular coloboma, heart defects, atresia of the choanae, retar-

dation of growth and development, and genitourinary and ear abnormalities CHARGE syndrome has rarely been associated with anterior pituitary dysfunction and with structural abnormalities of the pituitary gland only twice. We report the case of a child with CHARGE association and congenital hypopituitarism due to structural abnormalities of the pituitary gland.
Case presentation
The patient was a boy born with IUGR (birth weight 2020 gr, 37 weeks' gestation). Clinical features included retinal coloboma and micropthalmia, choanal atresia, dysplastic auricles with small accessory auricle, multicystic dysplastic kidney and hypospadias with cryptorchidism. Endocrine testing revealed central hypothyroidism and secondary hypoadrenalism. There was inadequate response to low-dose intravenous Synacthen stimulation test, with serum cortisol peaking at 10.3 µg/dl at 1 hour. He was started on thyroxine and hydrocortisone replacement, with hydrocortisone replaced first and thyroxine after a couple of days. Because of severe growth impairment by the age of 3.4 years (HSDS:–4.71, HVSDS: –3.62), growth hormone secretion was evaluated. A severe GHD was detected (peak GH 1.56 ng/ml in both tests) and rhGH therapy was initiated. MRI revealed ectopic posterior pituitary, without clinical significance.
Conclusion
We describe the case of a boy fulfilling criteria of CHARGE association[1,2] presenting with multiple anterior pituitary hormone deficiencies and structural pituitary abnormality. To our knowledge this is the 3rd case in the literature where congenital hypopituitarim in CHARGE syndrome is associated with pituitary structural abnormalities and especially ectopic posterior pituitary.
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AEP765

Controversies in the spectrum of GH-IGF-I axis disorders requiring replacement therapy

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Background
Growth hormone deficiency (GHD) is the most frequent endocrinological disorder inchildren with short stature, but there are significant controversies in the diagnosis due to lack of reliablediagnostic criteria. Moreover, at final height (FH) attainment, many subjects diagnosed withisolated GHD re-test normal. It is not clear whether this represents a form of transient GHD or a false positive diagnosis during childhood.
Aim
To evaluate differences in long-term outcomes (height gain □HT at FH) and retesting results in 57 GHD children (M=34, 59.6%) according to biochemical diagnosis: Group A (n=25) with max GH peak at stimulation test<8 µg/l, Group B (n=19) with max GH peak between 8 and 10 µg/l and Group C (n=13) with mean GH<3 µg/l (neurosecretory dysfunction, NSD). At FH all patients underwent to retesting after at least 1 month off therapy. Median GH dose at FH was 0.025 mg/kg/day.
Results
40/57 (70.2%) were pre-pubertal at diagnosis and showed a FH of –1.22±0.93 SDS not significantly different in the three groups (P=0.14) with a satisfactory □HT at FH of 1.37±1.00 SDS (P=0.08). Nonetheless, Group B showed the highest percentage of "poor responders" with 46% patients with □HT FH<1SDS (vs 13% and 12% in Group A and C, respectively) and with 25% children not reaching Mid-parental height (MPH) vs 6% and 0% in Group A and C, respectively. At linear regression, low HT SDS (P=0.0006), MPH difference (P=0.0039) and low IGF-I SDS at baseline (P=0.0035) were the most important predictive factors of □HT at FH. At FH attainment, GHD was reconfirmed in 28% (7/25), 10% (2/19) and 8% (1/13) patients in Group A, B and C, respectively.
Conclusion
A reduction of diagnostic cut-off at GH stimulation tests could better discriminate between "good" and "poor responders" and predict the persistence of GHD through transition. Nonetheless, GHD diagnosis solely based on provocative tests could exclude patients that might benefit of GH treatment. Group C response along with the predictive value of baseline IGF-I SDS bring back to lightNSD: should we consider an underlying hypothalamic derangement when the clinical presentation is strongly consistent with GHD-but pharmacological stimulation test is normal?
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AEP766

Severe heart failure in a young male patient with unrecognized hypopituitarism consequent to hemorrhagic fever with renal syndrome and undiagnosed hemochromatosis

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Background
The partial or complete hypopituitarism is described as late complication of hemorrhagic fever with renal syndrome (HFRS). Imaging methods of pituitary gland examination in the chronic phase showed pituitary atrophy, but a precise pathogenic mechanism that causes pituitary damage in HRFS remains unclear. While hypopituitarism in HFRS is rarely described, cardiac failure as a known complication of hypopituitarism is even more rarely described. We present a case of severe heart failure in a young male patient with unrecognized hypopituitarism consequent to HFRS and undiagnosed hemochromatosis.
Case Presentaton
42-year-old male patient was admitted at the Department of Endocrinology of University Clinical Centre of Republic of Srpska with suspected hypopituitarism. He managed to walk with the help of another person, and his speech was incoherent and with difficulties. The patient was pale, facial and body hairless with adynamia, myxedema, hypotension, and bilateral gynecomastia with decreased libido and impotency. Echocardiography verified a global reduction in myocardial contractility, dilated left atrium and ventricle, with low ejection fraction (10–15%). Results of hormone tests confirmed diagnosis of panhypopituitarism , and replacement therapy (hydrocortisone, levothyroxine and testostreone) was started. MRI of the pituitary gland was performed and it showed an "empty sella". On the third day after the therapy was introduced, the patient started to speak clearly and mental status was stabilized. The patient was independently mobile after seven days. Echocardiography performed a month after the replacement therapy was introduced showed an improvement in myocardial contractility with normal dimensions of the atrium and ventricle and estimated EF of 40%. Additionally, the diagnose of chemochromatosis was confirmed by genetic analysis of the HFE gene and presence of homozygosity for mutation pH63D (c 187>G), but the specific therapy was not initiated. At follow-up visit, 6 months after introduction of replacement therapy, the patient felt well, performed usual physical activities, male type of facial and body hair distribution recovered, his sexual function normalized, and he had a normal mental status. Echocardiography was completely normal 6 months after introduction of replacement therapy (the left ventricle with normal dimensions, EF 58%).
Conclusion
The heart failure is extremely rare complication of hypopituitarism, but it is usually reversible when hormonal therapy is replaced. According to significant relationship and a high prevalence of hypopituitarism as a consequence of HFRS, endocrinological investigation should be considered in patients with HFRS and clinical signs and symptoms suggestive of hypopituitarism.
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AEP767

Severe hyponatremia revealing hypopituitarism of undetermined etiology

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Introduction
Hyponatremia represents a frequent electrolyte disorder. It is defined as a serum sodium level below 135 mmol/L and it is severe when serum level is below 125 mmol/l. Endocrine disorders including adrenal deficiency and hypothyroidism are uncommon causes of hyponatremia. Secondary adrenal insufficiency is related with hyponatremia through increased ADH secretion. Herein, we report a case of severe hyponatremia revealing hypopituitarism.
Observation
A 35-year-old patient was admitted for a severe hyponatremia. His past medical history was unremarkable. He presented with headaches, weight loss and asthenia without visual disturbances or digestive signs. On physical examination, he had an altered general condition, pallor, a dry skin, a body weight of 61 kg, a body mass index of 23.5 kg/m^2, a blood pressure of 80/50 mmHg, a heart rate of 88 beats per minute, a psychomotor retardation and a dysarthria. The rest of the examination was unremarkable. On blood tests, he had a glucose level of 0.77 g/l , a sodium level of 111 mmol/l, a potassium level of 4.3 mmol/l, a creatinine level of 7 mg/l, a cortisol level of 0 ng/ml, a FT4 level of 0.48 ng/dl (nr: 0.7–1.5), a TSH level of 0.91 mIU/l (nr: 0.35–4.94), a LH level of 1.34 IU/l (nr: 1.14–8.75), a FSH level of 2.4 IU/l (norms: 1.37–21.63), a testosterone level of 14 nmol/l (nr: 10-32) and a prolactin level of1 µg/l (nr: 1.8–29.2). The diagnosis of acute pituitary insufficiency was established and the patient was put on hydrocortisone and then on L-thyroxine. The outcome was marked by the disappearance of the symptoms and the normalization of the natraemia. Initial pituitary magnetic resonance imaging (MRI) revealed a thickened pituitary stalk, an ectopic posterior lobe and an intrasellar process. The second MRI performed 18 days later, showed a pituitary necrosis and a partial empty sella with an optic chiasm ptosis. Immunological investigations revealed the presence of atypical ANCA. Other etiological tests were negative.
Conclusion
Our case represents an unusual cause of severe hyponatremia. In addition, the finding of atypical ANCA in etiologic investigations of hypopituitarism is not common. They are probably suggestive of an autoimmune disorder despite the lack of specificity.

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AEP768

A case of isolated ACTH deficiency and autoimmune pancreatitis associated with pembrolizumab treatment

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Background
Endocrine-related adverse effects of immune check-point inhibitors (ICIs) have been identified in growing number of cancer patients.
Case Presentation
A 49-year-old male with laryngeal cancer applied to ouroutpatient clinic with weakness, loss of appetite, weight loss, nausea and vomiting for the last three weeks. He was diagnosed with T3N1M0 laryngeal squamous cell cancer seven months before this admission and was given concurrent cisplatin and radiotherapy, and he had just received 10th cycle of his pembrolizumab (200 mg every 3 weeks) treatment. He was not given glucocorticoids alongside of pembrolizumab. Physical examination was normal except low blood pressure (90/70 mmHg). Laboratory exam revealed normal serum sodium, potassium and plasma glucose levels. Morning serum cortisol (0.47 mcg/dl) and ACTH(10.1 pg/ml) levels were low. TSH, fT4 and fT3 levels were 6.3 uIU/ml, 11.8 pmol/l and 4.7 pmol/L respectively, showing an increase in TSH from pre-treatment level of 1.6 uIU/ml. Thyroid autoantibodies were negative, and thyroid parenchyma was normal on ultrasound, displaying an incidental nodule with benign ultrasonographic characteristics. Other hormonal axes of anterior pituitary were intact. Pituitary MRI revealed enlarged pituitary gland without infundibular thickening, and loss of posterior pituitary bright spot. He had no symptoms or laboratory signs indicative of diabetes insipidus. Accordingly, a diagnosis of hypophysitis with isolated ACTH deficiency (IAD) secondary to pembrolizumab was made. Oral prednisone in a dose of 10 mg/day was started and tapered down to 5 mg/day in three days which improved symptoms dramatically. Levothyroxine was not started since thyroid function tests turned back to normal during follow up. However, the patient was admitted to our hospital one month later due to severe epigastric pain, nausea, vomiting, and elevated serum amylase, lipase and liver function tests. CT displayed oedematous pancreatic enlargement with increased density, without necrosis. Acute cholecystitis and pancreatitis due to bile duct stones were ruled out. The patient was diagnosed with autoimmune pancreatitis and started on 48 mg/day methylprednisolone which improved symptoms and laboratory signs. Pituitary MRI findings were stable 3 and 6 months after the diagnosis of hypophysitis, however local relapse of laryngeal cancer emerged 6 months following the cessation of pembrolizumab.
Conclusions
The risk of IAD has been reported to be higher in patients using ipilimumab or combined ICI therapies, but few cases were defined who were receiving pembrolizumab treatment only. Our patient also had autoimmune pancreatitis, which is reported to occur less than 1% of pembrolizumab treated patients.

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AEP769

Empty sella: Who thinks of it while studying hyponatremia?

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Hyponatremia is a common disorder, especially among the elderly, and an important morbidity and mortality cause. Empty sella syndrome, on the other hand, is a rare entity, more common in women between their fourth and sixth decade of life, and endocrine dysfunction has been reported in 10–60% of the cases. A 68-year-old man, with a past medical history of essential hypertension and glaucoma, presented at the emergency room due to malaise, asthenia, somnolence and anorexia for the previous 2 days. He had a prior history of respiratory tract infection and had been started on amoxicillin/clavulanic acid and azithromycin six days before. At admission he was vigil but lethargic, his blood pressure was 138/72 mmHg, heart rate 78 beats/min, body temperature of 36.4 ºC. He was pale, presented with hair weakening, mainly on his eyebrows from which the external third was missing. The blood chemistry revealed severe hyponatremia (108 mmol/l), normal potassium levels (4.4 mmol/l), a reduced serum osmolarity (220 mosmol/l), and 84 mg/dl of blood glucose. While at the emergency room IV isotonic fluids were started with poor clinical response. Hyponatremia hormonal investigation revealed ACTH 9.7 pg/ml (in the afternoon) and 8.2 pg/ml (in the morning), serum Cortisol 3.61 ug/dl (in the afternoon), THS of 16.56 mUI/l and FT4 of 2.2 pmol/l. Pituitary basal function tests were completed with FSH 3.2 mUI/ml, LH 1.3 mUI/ml, Prolactin 2.0 ng/ml, Testosterone 121 ng/dl, IGF-1 27 ng/ml, and hHG < 0.05 ng/ml. Brain MRI showed an empty sella (with a flattened pituitary gland). Hypothyroidism, adrenal insufficiency and hypogonadotrophic hypogonadism were diagnosed. Patient was started on hormonal replacement treatment with prednisolone 5 mg/day and levothyroxine 0.075 mg/day, and discharged at the 8th day, asymptomatic with sodium levels of 128 mmol/l. In the follow-up visit, after obtaining normal levels of PSA and a normal prostatic ultrasound, testosterone was also initiated. Sodium levels were already within normal range (135 mmol/l) and prednisolone was titrated to 2.5 mg/day. This clinical case illustrates an unusual presentation of hyponatremia as the first sign of hypopituitarism, showing the relevance of etiology investigation of electrolyte disorder for its adequate treatment.

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AEP770

Massive pulmonary embolism in a newly diagnosed acromegaly patient

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Introduction
Acromegaly is caused by growth hormone (GH) and insulin-like growth factor (IGF-1) excess and leads to various comorbidities. However, the association between acromegaly and thromboembolic diseases is unclear. Herein, we present a newly diagnosed acromegaly patient with massive pulmonary embolism.
Case report
A 61-year-old female was hospitalized with acromegaly pre-diagnosis. She complained about extensive arthralgia and snoring. She had hypertension,

prediabetes, and vertigo in personal history. Her medications were amlodipine/valsartan and betahistidine. Her blood pressure was 130/80 mm/Hg and body mass index was 36.21 kg/m^2. The physical examination was unremarkable out of acral enlargements and macroglossia. Baseline serum IGF-1 was 538 ng/ml and GH was 2.85 ng/ml. Nadir GH level after glucose tolerance test was 1.68 ng/ml. Magnetic resonance imaging of the pituitary gland showed a 6-mm sized microadenoma. There was no pathological finding on the electrocardiogram and echocardiography. A sleep study confirmed sleep apnea syndrome. During hospitalization, she complained about a cough. Breathing sounds decreased while arterial oxygen saturation and chest radiography were normal. The patient consulted to pulmonary diseases department. The thorax tomography (CT) showed massive pulmonary embolism in bilateral main pulmonary arteries. 2 × 0.8 IU/day DMAH treatment was initiated in the acute period because she was clinically stable and followed by long-term anticoagulation therapy with warfarin. Lanreotide 90-mg was started instead of a pituitary surgery because of the high operation risk. Venous doppler ultrasonography, which was performed for excluding a deep vein thrombosis was unremarkable. Anti-nuclear antibody, protein C and S, fibrinogen, and anti-cardiolipin Ig-M and G were normal. Malignancy screening for breast, colon, and thyroid was also negative. Factor II was heterozygote and MTHFR (C677T) was homozygote in the thrombophilia screen. Bilateral pulmonary arteries were observed normally in the sixth month of warfarin therapy. We continue to follow up patient with normal GH and IGF-1 levels under lanreotide treatment.

Discussion

Although there are no clear data on whether acromegaly is a hypercoagulable condition or not, a few cases have been reported. Some studies demonstrated that serum coagulation markers altered in acromegaly. Besides active acromegaly, some comorbidities like sleep apnea syndrome and malignancies can contribute to hypercoagulability risk. Similar to our case, inherited hypercoagulability conditions accompanied by acromegaly in some of the reported cases. In conclusion, thromboembolism can be seen in acromegaly patients rarely, especially in those having additional risk factors.

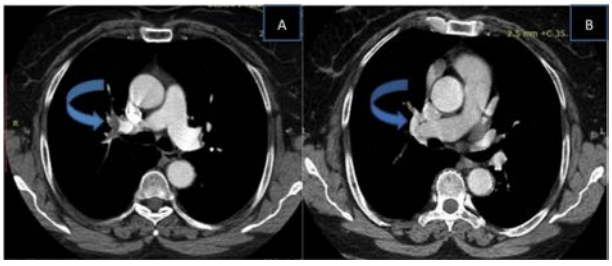

Figure 1 CT showing filling defects in pulmonary arteries (A) and normal appearance after treatment (B).

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AEP771

Persistent hypercortisolism due to cushing disease

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Background

Cushing's disease (CD) develops as a result of ACTH-secreting pituitary adenoma. Transsphenoidal selective surgery (TSS) is the first-line therapy, and success is largely determined by the experience of the surgeon. There are several reasons for the persistence of the disease, but it is almost impossible to predict such an outcome in advance, which leads to multiple interventions and has a pronounced effect on the quality of life of patients.

Clinical case

A 33-year-old female addressed the clinic with typical symptoms of hypercorticism in October 2018. From the history: in 2016, ACTH-dependent hypercortisolism was revealed, but pituitary MRI showed no pathology. It was recommended to repeat the MRI after 6 months. She returned 2 years later due to poor health, diagnosed with CD (24hr urinary cortisol – 799 nmol/day (< 400), 1 mg dexamethasone suppression test (DST): 14.20 µg/dl (< 1.8); ACTH–71 pg/ml (< 46); 8 mg dexamethasone suppression test: cortisol was suppressed from 18.67 µg/dl to 1.99 µg/dl; MRI scan: pituitary microadenoma 4 × 3.2 mm). Although treatment at an expert level institution was recommended, the patient preferred a center that doesn`t belong to the institutions with the greatest experience in treating CD, where a TSS was performed on 09/17/18. Immunohistochemically (IHC): pituitary adenoma with expression of ACTH, GH, PRL. Post-operatively, remission didn`t occur (plasma cortisol – 732 nmol/l (< 536); ACTH-76 pg/ml), secondary hypothyroidism was detected. She was offered an immediate hypophysectomy, which she refused. Ketoconazole 200 mg/d, cabergoline 0.5 mg 2 times/week, levothyroxine 50 mg/day were prescribed. After discharge, she turned to the clinic to determine further tactics. Physical examination data corresponded to CD, persistent hypercortisolism was biochemically confirmed. MRI scan: pituitary microadenoma 5×5, 5×4 mm with postoperative changes. For TSS, she was referred to an expert level center, however, on the recommendation of a neurosurgeon, the operation was postponed due to predicted inefficiency. The maximum tolerated dose of ketoconazole was selected: 600 mg/day, which didn`t allow achieving eukortisolism: plasma cortisol - 1265 nmol/l. TSS was performed after excluding ACTH-ectopic tumors according to the results of petrosal sinus sampling, post-operatively, remission didn`t occur (IHC: intensive diffuse expression of ACTH). Currently, the patient is preparing for radiation therapy.

Conclusion

Treatment of patients with CD should be carried out exclusively in an expert level center. Studies are needed aimed at determining the risk of persistent CD to optimize treatment and reduce the time of persistence of hypercortisolism, the number of hospitalizations, economic costs and improve the quality of life of patients.

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AEP772

The effect of chronic glucocorticoid exposure on brown adipose tissue in patients with cushing's disease

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Objective

Various effects of glucocorticoids occur in brown adipose tissue depending on their duration of action. As a result of exposure to glucocorticoids, thermogenesis and oxygen use in brown fat tissue are reduced in animal studies. In this study, we aimed to compare the levels of UCP1 (uncoupling protein 1), Irisin, BMP 7 (bone morpogenic protein), PRDM16, which are brown addipose tissue markers, between patients with Cushing's disease and healthy controls

Methods

This study included 48 patients with Cushing's disease and 40 non diabetic controls who met the inclusion criteria. Cushing syndrome was ruled out by performing 1 mg dexamethasone suppression test to individuals in the control group. Fasting blood samples were analyzed by Enzyme-Linked Immunosorbent Assay method for UCP1, Irisin, BMP 7 and PRDM 16. Demographic and clinical information was also recorded.

Results

There were 11 men (22.9%), 37 women (77.1%) in the patient group; 9 men (22.5%) and 31 women (77.5%) in the control group. Body mass index was 31.29±5.76 kg/m^2 in the patient group, and 33.42±3.11 kg/m^2 in the control group (P<0,05). HbA1c and triglyceride levels were statistically significantly higher in patient group than in the control group (P<0,05). PRDM16, Irisin, BMP7, UCP1 levels were not significantly different between the two groups (P>0,05). Macroadenoma was detected in 19 (40.4%) patients and microadenoma in 28 (59.6%) patients in the Cushing disease group. Mean irisin, PRDM16 and BMP7 levels were similar in microadenoma and macroadenoma groups (P>0,05). However, UCP1 was significantly higher in microadenoma group than macroadenoma group (P <0.05). There was a positive correlation between serum cortisol (morning and midnight cortisol) with irisin (P<0.05), but no correlation with other markers (P>0.05). Also a positive correlation was observed between urine free cortisol and UCP1 levels (P<0.05).

Conclusion

Short term exogenous glucocorticoid administration showed decreased levels of brown adipose tissue markers in animal studies. Opposite of this in our study, there was no difference between the patient and control groups in terms of brown adipose tissue markers. However,in patients with Cushing's disease, UCP 1 and BMP7 were significantly correlated with increased cortisol levels. This finding may suggest that, prolonged exposure of high levels of endogenous cortisol causes loss of adipose tissue functionality by

creating invivo resistance. It is obvious that detailed studies are needed to explain the effects of chronic cortisol exposure.

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AEP773

A rare outcome after surgical removal of insulinoma- case presentation

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Introduction
Insulinoma is a rare tumor that causes spontaneous fasting hypoglycemia in a supposedly healthy adult. Mostly these tumors are single and benign, few are malignant and a minority is represented by multiple adenomas. The treatment of choice is surgical removal of the insulinoma, which cures the condition in the majority of cases. However, after performing the surgery, less than 10% of patients either develop diabetes mellitus or continue to have persistent hypoglycemia.
Case presentation
Patient, male, 68 years old, with history of high blood pressure and ischemic stroke, presents for a month the following: diaphoresis, dizziness, altered general state, relieved by carbohydrates intake. Five days before admission in our service, he presented acute symptoms and a fingerstick blood glucose level of 25 mg/dl. During his hospital stay, he did not tolerate the fast and repeated blood samples showed low laboratory glucose and elevated plasma insulin (up to 1000 uU/ml). Further hormonal tests excluded MEN1 syndrome. The CT scan identified one small tumor located in the body of the pancreas. The patient was referred to surgery and distal subtotal pancreatectomy was performed (intraoperative ultrasound confirmed the tumor). TNM staging fits the tumor as pT1N0 and histopathological examination confirmed the neuroendocrine tumor of the pancreas, well-diferentiated (G1). After surgery the general condition of the patient was improved, but he started to present alternating episodes of mild hyperglycemia and hypoglycemia with elevated plasma insulin. The post-operative MRI scan showed no residual tumor or other pancreatic lesions. "Whole-body" somatostatin receptor scintigraphy (99mTc-Tektrotyd) with the addition of SPECT-CT was performed and it revealed a small nodule with intense uptake, in the most caudal part of the pancreas. The patient is scheduled for the second intervention.
Conclusions
The peculiarity of the case is represented by the unstable metabolic balance: the patient developed post-pancreatectomy diabetes mellitus, but in the presence of the second (previously unsuspected) insulinoma this translated into fluctuations of glycemia around normal levels (both hypo- and hyperglycemia) in the absence of treatment.

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AEP774

Evaluation of factors associated with presence and growth of thyroid nodules in patients with acromegaly

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Objective
To investigate factors associated with the presence and growth rate of thyroid nodules(TN) in patients with acromegaly.
Methods
We retrospectively evaluated the medical records of 52 patients with acromegaly followed in our institution (University Hospital Ramón y Cajal). The frequencies of TN and papillary thyroid cancer (PTC) and potential factors associated with nodular thyroid disease (NTD) were investigated. In patients with NTD ($n=25$) the first and last ultrasound performed were evaluated. The mean follow up period in these patients was 62.9 (S.D.=44.4) months. The changes in nodule size comparing with the initial study and the potential factors affecting nodule growth were investigated. The statistical analysis was performed with STATA15.0.
Results
The mean age of the cohort was 50.2 years (SD=15.90) and 71% ($n=37$) were females. At diagnosis, 48.1% of the patients had TN (21 females/four males), and the mean size of the dominant nodules (MSN) was 16.1 (S.D.=13.013) mm. TN were more commonly found among women (56.8% vs 26.7%, $P=0.049$), and patients with IGF1 above the upper limit of normal (ULN) (71.4% vs 28.6%, $P=0.043$). No associations were found with age ($P=0.769$), IGF1 levels ($P=0.127$), macroadenoma ($P=0.089$), surgical cure ($P=0.76$), thyroid function($P=0.612$), obesity ($P=0.792$) or other comorbidities. No correlation was found between MSN and IGF1 or TSH levels ($P>0.05$ for r2). During follow up, the mean nodule growth was 1.5 (S.D.=8.38) mm, the mean nodule growth/year was 1.40 (S.D.=4.91) mm, and only 5 patients experienced significant growth (> 2 mm) at the end of the follow up. At last visit, nodule growth was similar in uncured vs cured patients ($P=0.317$). Neither differences were found according to thyroid function ($P=0.122$) or months with IGF1 above normal range ($P=0.057$). No correlations were found between growth and IGF1 at the time of ultrasounds($r_2=0.429$, $P=0.126$), thyroid function ($r_2=0.055$, $P=0.851$) or other parameters. At diagnosis fine needle aspiration (FNA) cytology was done in 13 patients, 11 were classified as benign (Bethesda category II, B2) and 2 as atypia of undetermined significance (Bethesda category III, B3). During follow up, FNA was repeated in 5 patients: cytology was B2 in all 3 patients with initial B2 rebiopsied due to significant growth, and remained indeterminate(one B3 and one B4) in the two nodules with initial B3 cytology. Seven patients were operated: 4 due to compressive multinodular goiter, 1 due to significant TN growth (+29 mm), and 2 due to indeterminate cytology. PTC was diagnosed only in the B3 patient (microPTC).
Conclusion
We found that NTD is frequent in acromegalic patients, especially in women and patients with elevated levels of IGF1. During follow up, TN growth was infrequent and seemed to be unrelated to acromegaly activity status and thyroid function. The prevalence of PTC was 1.9% in our acromegaly cohort.

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AEP775

FSH levels are related to E-cadherin expression and subcellular location in non-functioning pituitary neuroendocrine tumours

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Objectives
To study the effect of epithelial-to-mesenchymal transition (EMT) on hormone expression in gonadotroph non-functioning pituitary neuroendocrine tumours (NF-PitNET).
Background
Gonadotroph PitNETs can express FSH and LH or be hormone negative, however they rarely secrete hormones. During tumour development, epithelial cells develop a mesenchymal phenotype. This process is characterised by decreased membranous E-cadherin and translocation of E-cadherin to the nucleus. Further, oestrogen receptors (ER) regulate both E-cadherin and FSH expression and secretion. Whether the hormone status of patients with gonadotroph PitNETs are regulated by EMT and oestrogen receptors is uncertain.
Methods
Retrospective study of 105 gonadotroph PitNETs. Immunohistochemical analyses and real-time-qPCR for FSH, LH, E-Cadherin and ERα were performed. Blood samples, clinical data and radiological findings were analysed.
Results
NF-PitNET with high FSH expression had decreased immunohistochemical staining for membranous E-cadherin ($r=-0.384$; $P<0.0001$) and increased staining for nuclear E-cadherin ($P<0.0001$). Further, high FSH expression was associated with increased ERα staining ($r=0.357$; $p=0.0002$) and mRNA ($r=0.331$, $P=0.0039$). Circulating levels of P-FSH correlated with FSH staining in NF-PitNET ($r=0.360$; $P=0.0025$). Tumour size and invasiveness was not related to FSH staining, E-cadherin or oestrogen receptor. LH expression in tumours were not associated with E-cadherin or ERα. In gonadotroph PitNETs, FSH staining is associated with decreased membranous E-cadherin and nuclear translocation of E-cadherin. FSH correlates with expression of oestrogen receptors and circulating P-FSH. Further studies are needed to understand the mechanisms behind these findings.

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AEP776

To optimize the acute octreotide suppression test in predicting the efficacy of long acting somatostatin analogues in acromegaly

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A 6-hour octreotide suppression test (OST) is useful in the selection of patients with acromegaly for chronic somatostatin depot analogues treatment. However, it is time consuming and that brings inconvenience to patients. We aim to simplify the blood sampling of OST, and determine the reliability of a short version of the classic 6-hour OST. The data provided in the supplementary tables of the primary manuscript were used to re-analyze the efficacies of the simplified OST tests. SPSS Software Version 25 was used for data analyses. To find the best receiver operating characteristic (ROC) curve, several analysis of the shorten-test (including 2-hour, 3-hour, 4-hour and, 6-hour's tests) were performed, and compared the parameters of ROC with that of 2-day's examination to find a proper shorten test period. After calculating, □GH (0–3 h) more than 80.51% and 91.84% provided the best predictors of a good GH response (sensitivity 96.9%, specificity 85.7%) and a good IGF-1 response (sensitivity 86.7%, specificity 81.3%). □AUC (0–3 h) more than 71.07% provided the best predictor of a good tumor size response (sensitivity 81.8%, specificity 90.6%). From these results, we conclude that OST could be simplified as the 3-hour measurements. The □GH (0–3 h) is the best optimistic parameter to predict a good GH, or IGF-1, response, while the □AUC (0–3 h) is the best for a good tumor size response to short-term efficacy of SSA in acromegaly.

Keywords: acromegaly, somatostatin analogues, remission prediction, octreotide suppression test.

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AEP777

Acromegaly is associated with reduced socioeconomic status and more so in female patients: A nationwide population-based study

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Context
Acromegaly is a rare and insidious disease associated with severe somatic morbidity but data on socioeconomic status are scarce.
Objective
To study the socioeconomic status in acromegaly in a population based, nationwide follow-up study.
Patients and methods
All incident cases of acromegaly (n=576) during the period 1997–2010 were included, representing 10.116 years at risk. For every patient, 100 persons were sampled from the general population matched on date of birth and gender (comparison cohort). Cox regression and hazard ratios (HR) or conditional logistic regression with 95% confidence intervals (CI) were used.
Main outcome measures
Annual income, allocation of cash benefits, retirement, cohabitation, separation, parenthood and education level.
Results
The proportion of retirement was significantly increased in patients with acromegaly after the time of diagnosis (HR 1.43, CI95% 1.26–1.62) and also during the 5-year pre-diagnostic period (HR : 1.15, CI95% 1.03–1.28). The utilisation of cash benefits was increased in patients with acromegaly in the period preceding the time of diagnosis. Among patients who maintain a paid job, the annual income was similar to the reference population. Compared with the background population, cohabitation was less prevalent (HR : 0.69, CI : 0.50–0.95) as was parenthood (HR : 0.56, CI : 0.39–0.80), whereas neither educational level (HR: 0.61, CI : 0.35–1.06) nor the prevalence of separation (HR : 1.13, CI : 0.86–1.47) weredifferent in acromegaly. A reduced socioeconomic status was present before the diagnosis of acromegaly. Female gender was associated with a significantly worse socioeconomic status (Table 1).

Tabel 1 Hazard ratios of the various outcomes.

After diagnosis	Female	*P*-value	Male	*P*-value
Mortality	1.56 (1.27–1.91)	< 0.01	1.32 (1.09–1.61)	< 0.01
Retirement	1.58 (1.33–1.87)	< 0.01	1.30 (1.08–1.55)	< 0.01
Education	0.65 (0.34–1.25)	0.19	0.52 (0.17–1.63)	0.26
Separation	1.28 (0.89–1.83)	0.18	0.99 (0.67–1.47)	0.95
Cohabitaion	0.62 (0.38–1.00)	0.05	0.76 (0.50–1.16)	0.20
Parenthood	0.33 (0.17–0.67)	< 0.01	0.74 (0.48–1.12)	0.16
5-years pre-diagnosis				
Retirement	1.14 (0.98–1.33)	0.08	1.16 (0.99–1.36)	0.07
Cohabitaion	0.75 (0.53–1.06)	0.10	1.06 (0.79–1.41)	0.71
Parenthood	0.55 (0.34–0.87)	0.01	0.82 (0.60–1.13)	0.23

Conclusion
1. Socioeconomic status is impaired in patients with acromegaly even before diagnosis. 2. Females and patients without disease remission have significantly worse outcomes. 3. Early diagnosis and effective treatment are essential not least in female patients.

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Reproductive and Developmental Endocrinology

AEP778

Case-control study on ACE2 expression in children with short stature

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Background
Short stature is one of the most common presentations to paediatric endocrinologists. It is estimated that despite all the exams, in 50–90% of cases, children are labelled as having idiopathic short stature. It has been recently reported that genetic ACE2 deficiency is associated with reduced body weight as well as with impaired gestational weight gain and fetal growth restriction in pregnancy. It has been argued that ACE2 deficiency, which is usually associated with an increase of tissue Angiotensin II, could be associated with prenatal as well as postnatal changes leading to reduced growth (such as uterine artery dysfunction and IGF-1 reduction, respectively). Based on these premises, the aim of our study was to evaluate whether there was a difference of ACE2 expression in children with short stature as compared to age-matched controls.
Methods
We designed an exploratory case-control study aiming at recruiting consecutively 40 children with short stature (cases) and 40 controls presenting at the Endocrinology Service, aged 2–13 years, excluding those with acute intercurrent diseases, diabetes, renal insufficiency, syndromes and/or on medications. After signing the informed consent to participating in the study, children underwent a medical visit and a fasting blood sampling. Peripheral blood mononuclear cells (PBMC) were isolated to extract mRNA for gene expression analyses. Sera were collected for protein measurements.
Results
Children with short stature (n=17) presented with lower height and body weight as compared to controls (n=18). Our preliminary data show that children with short stature exhibited a significant reduction of ACE2 gene expression, and a significant increase of ACE/ACE2 ratio in PBMC. This was associated with a modest increase of Angiotensin II/Angiotensin 1–7 ratio. Our multivariate analysis showed that across the groups ACE2 was independently associated with height but not with body weight.
Conclusions
To our knowledge, this is the first study investigating ACE2 expression ina paediatric population. Our preliminary results, showing that ACE2

expression is significantly reduced in children with short stature, are in line with the literature. This study could representthe basis for further investigations aiming at establishing the presence of a causal relationship between ACE2 deficiency and growth reduction, with further diagnostic and therapeutic perspectives

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AEP779

Coagulation abnormalities in patients with klinefelter syndrome compared to age-matched healthy controls: Cross-sectional assessment by thrombin generation test

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Introduction
Klinefelter syndrome (KS) is known to be associated with an increased risk of venous thromboembolism and arterial thrombosis, but the aetiology behind this prothrombotic status has not been fully elucidated. The aim of this study was to cross-sectionally investigate the coagulative state in subjects with KS compared to age-matched healthy males.
Methods
Coagulation factors assessment, clinical characteristics collection and thrombin generation test (TGT) were performed in 58 consecutive KS patients and 58 controls. TGT is based on the continuous registration of thrombin generation (mediated by procoagulants) and decay (mediated by anticoagulants) using a fluorogenic substrate. The curve of thrombin concentrations (vertical axis) by time (horizontal axis) is called *thrombogram* and is described by the following parameters: *lag-time* (time from coagulation ignition to the formation of the first amounts of thrombin); *thrombin-peak* and *time-to-peak*; *endogenous thrombin potential (ETP*, the area under the thrombin curve, measured with and without the addition of thrombomodulin); the *ETP-ratio* (ETP with/ETP without thrombomodulin), that may be considered the best parameter through which *in vivo*subtle procoagulant imbalance can be detected.
Results
No statistically significant difference was found between KS patients and healthy subjects in lag-time, thrombin-peak, time-to-peak or ETP; however, the ETP-ratio was significantly higher in KS compared to controls (0.73 and 0.66 respectively, $P<0.001$). KS patients had higher circulating concentrations of Factor VIII ($P=0.001$) and Fibrinogen ($P<0.001$) and a higher Factor VIII/Protein C ratio ($P=0.018$), while platelet count, PT ratio, aPTT ratio, Factor II, Protein C and Antithrombin were similar in the two groups. ETP-ratio was positively correlated with Factor VIII concentrations ($P=0.007$, $\rho=0.355$) and showed a trend of association with impaired fasting glucose ($P=0.069$) and Factor VIII/Protein C ratio ($P=0.072$, $\rho=0.240$). Fibrinogen levels were positively associated with age ($P=0.004$, $\rho=0.401$), body mass index ($P=0.001$, $\rho=0.468$) and fasting plasma glucose ($P=0.049$, $\rho=0.356$), while FVIII did not show any correlation with metabolic parameters as well as age. Testosterone replacement therapy and smoke were not associated with any of the coagulation parameters.
Conclusion
As clinically suggested, a procoagulant imbalance is present in KS subjects and is possibly related to higher Factor VIII concentrations here demonstrated. While testosterone replacement therapy and smoking habit did not show a significant impact, other typical factors associated with thrombotic risk such as advanced age, BMI and altered glucose metabolism could further increase this imbalance by determining hyperfibrinogenemia.

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AEP780

Radioidine (RAI) as a new therapy for the treatment of ovarian cancer through the sodium/iodide symporter (NIS)

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Introduction
Ovarian cancer is the most lethal gynecological malignancy. Early diagnosis has a survival rate of 90%. Unfortunately, more than 70% of cases are diagnosed when the cancer has already metastasized, and survival rates do not exceed 30% in these cases. The sodium iodide symporter (NIS) is an integral plasma membrane glycoprotein expressed in the basolateral surface of the thyroid gland, where it mediates active transport of iodide. Radioiodide therapy (RAI) through NIS is the most effective therapy in thyroid cancer. Our group has demonstrated that NIS is expressed in ovarian surface epithelium and is overexpressed in human epithelial ovarian cancer, establishing NIS as a tumor marker. The aim of this study is to determine whether endogenous expression of NIS in ovarian cancer can be used as therapeutic tool using-RAI in ovarian tumors.
Materials and methods
serous ovarian cancer cell line (SKOV3) was transfected permanently with exogenous NIS (SKOV3-hNIS) and in vitro characterized by different techniques (western-blot, PCR, flow cytometry, immunofluorescence, iodide uptake). In vivo, NIS-transfected and not transfected cells were injected into flanks of nude and NSGs mice. NIStumor expression was analyzed by different techniques and NIS functionality in animal models was measured by SPECT-CT.^{131}I treatment was tested in subcutaneous nude female mice. Human ovarian tumors samples received from the Mostoles Hospital were disaggregated and used to produce primary cultures and PDX animals.
Results
PCR and western-blot show NIS expression in both in vitro (cancer cells) and in vivo (xenotransplanted cells in animal models and human samples). Immunofluorescence and immunohistochemistry show that NIS expression occurs in plasma membrane. In vitro and in vivo (SPECT-CT) Iodide uptake assays show that the expression of NIS in plasma membrane is functional. ^{131}I treatment in subcutaneous tumors show an overall decrease in tumor size of 71% vs a 632% increase in not treated tumors. We observed that more than 37% of tumors disappear in 25 days with just a single ^{131}I dose.
Conclusion
NIS expression in human ovarian cancer cell lines is functional in vitro and in vivo, targeted to the plasma membrane, and able to accumulate iodide. A single dose of ^{131}I reduces ovarian tumor growth in NIS-expressing tumors and is more effective than conventionally chemotherapy. Patient tumors are expressing NIS in the plasma membrane, which leads us to propose NIS as a therapeutic approach to the treatment of ovarian cancer through radio iodine.

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AEP781

Luteinizing hormone/choriogonadotropin receptor (LHCGR) mediates different kinetics of G proteins, β-arrestins and cAMP activation

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Pituitary luteinizing hormone (LH) and placental human choriogonadotropin (hCG) are two heterodimeric glycoprotein hormones regulating reproduction. They bind the same receptor (LHCGR) expressed in gonadal cells, activating hormone-specific G protein- and β-arrestins-dependent signaling cascades, before LHCGR internalization. LH induces preferential proliferative signals, while hCG activates mainly the steroidogenic pathway,

reflecting their physiological roles. In this study,we compared the kinetics of LH- versus hCG-mediatedG proteins and β-arrestin 2 activation *in vitro*. The HEK293 cell line was transiently transfected with the LHCGR-encoding plasmid, together with that encoding G proteins- or β-arrestin 2-tagged bioluminescence resonance energy transfer (BRET) biosensors. Cells were treated by various hCG and LH concentrations (pM-nM range) and the activation of Gαs, Gαq, Gαi protein and β-arrestins was evaluated by BRET, under native conditions or after inhibition of LHCGR internalization by Dynasore. We demonstrated that LH/hCG binding to LHCGR mediates the activation of G proteins and recruitment of β-arrestin 2 in a hormone-specific manner. LHCGR-Gαs protein interaction increased upon 10 nM hCG, but not LH treatment (one-way ANOVA; $P<0.05$; $n=8$), reflecting the previously demonstrated preferential activation of intracellular cAMP signaling by the placental hormone [doi:10.1210/er.2018-00065]. These data are confirmed by kinetics analysis intracellular cAMP increase over 120-min, which achieved higher levels upon treatment by hCG than LH when hormones are administrated to cells at the 50% effective concentration (EC50; hCG=100 pM; LH=500 pM; Kruskal-Wallis test, $P<0.05$; $n=4$). On the other hand, LH was more potent than hCG in promoting LHCGR-Gαi protein and LHCGR-β-arrestin 2 interactions, thus confirming preferential activation of proliferative signals (means±SEM one-way ANOVA; $P<0.05$; $n=8$) [doi:10.1210/er.2018-00065]. Interestingly, LH and hCG mediated similar kinetics of intracellular cAMP increase between 30–120 min, when LHCGR internalization is blocked by Dynasore, while short-term (0-30) min hCG-induced cAMP levels are anyway higher than those LH-mediated (Kruskal-Wallis test, $P<0.05$; $n=4$). These results suggest that endosomal compartmentalization of LHCGR is involved in the differentiation of the long-term LH/hCG-induced cAMP signaling.
We have demonstrated that LH and hCG drive LHCGR in hormone-specific interaction with Gαs and i proteins, as well as β-arrestin 2 and endosomal compartments, and resulting in different intracellular signaling patterns.

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AEP782

New data in turner syndrome: Results from a long-term prospective observational study from diagnosis to adulthood

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Turner syndrome (TS), one of the most frequent chromosomal aberrations in females, is characterized not only by structural abnormalities (somatic and congenital) but also by acquired comorbidities, such as metabolic disorders, cardiovascular alterations, autoimmune diseases, osteoporosis, and malignancies. The prevalence of structural abnormalities that usually complicate TS at diagnosis is well known. However, the prevalence of acquired complications, that may appear at any age during follow-up, is less known, for the scarcity of data available in literature in TS during adulthood. This limit does not allow to establish an exact flow-chart on how to monitor acquired pathologies in TS. This long-term prospective observational study has been performed in a population of 139 TS diagnosed and then followed at S. Orsola-Malpighi hospital of Bologna, firstly by pediatricians and secondly by endocrinologists, using the same structured protocol of follow-up. The mean age of diagnosis of TS was 9.52±8.09 years. The average duration of follow-up was 28.4±9.7 years. Therefore, the age at the end of follow up was 38.4±8.3 years. Diabetes was diagnosed by oral glucose tolerance test in 21 patients (15.1%) with a mean age at diagnosis of 39.0±10.9 years. Hypertension was discovered in 35 patients (25.2%) with a mean age at diagnosis of 31.1±10.0 years, one of these patients complicated with aortic dissection at age 45. During follow-up we diagnosed 104 autoimmune disorders with a mean age at diagnosis of 23.8±10.5 years; in particular, we found 81 cases of thyroiditis with or without hypothyroidism, 10 cases of coeliac disease, 3 cases of Basedow-Graves disease, 3 cases of alopecia areata, 2 cases of vitiligo, 2 cases of Sjogren syndrome, 1 case of psoriasis, 1 case of chronic atrophic gastritis and 1 case of Crohn's disease. Osteoporosis was detected in 28 patients (20.1%). Finally, we found 21 cases of malignancies with a mean age at diagnosis of 31.5±13.8 years; in particular, we found 7 cases of papillary thyroid carcinoma, 5 cases of nervous system tumors, 3 cases of skin tumors, 2 cases of gonadal tumors, 1 case of kidney cancer, 1 case of breast cancer, 1 case ofacute lymphoblastic leukemia, and 1 case of aggressive hemangioma. These data reinforce the need to monitor patients with TS lifelong, focusing on endocrine, metabolic, cardiovascular and oncological complications. A specific structured protocol is useful for early detection of such important complications.

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AEP783

Establishing an anti-müllerian hormone (AMH) cut-off to determine polycystic ovarian morphology (PCOM) supporting diagnosis of polycystic ovarian syndrome (PCOS): The APHRODITE study

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PCOS is a common pathology in women of reproductive age, and ~70% of affected women remain undiagnosed. Clinical features of PCOS include ovulatory dysfunction, hyperandrogenism and PCOM (Rotterdam criteria). Replacement of transvaginal ultrasound (TVUS) with a blood test for PCOM is clinically desirable, as lack of access to TVUS may contribute to underdiagnosis of PCOS. We aimed to derive and validate a cut-off for AMH to discriminate PCOM using the Elecsys AMH Plus immunoassay. APHRODITE is a case-control study of PCOS-positive (cases) and PCOS-negative (controls) women aged 25–45 years. Cases were defined using Rotterdam criteria, showing the full phenotype A (irregular cycles/ovulatory dysfunction, clinical or biochemical hyperandrogenism and PCOM); controls had an antral follicle count (AFC)≤20, based on the new international guideline for PCOS. The discovery cohort included 484 cases and 575 controls; the validation cohort consisted of 455 cases and 500 controls. Serum levels of AMH were measured using the Elecsys AMH Plus immunoassay, and AFC was determined by TVUS. An AMH cut-off was optimised in the discovery cohort based on concordance analysis. Performance (sensitivity, specificity and area under the curve [AUC]) of the defined cut-off was evaluated in the validation cohort. Exploratory analyses in different sub-cohorts (including age groups) were performed. Compared with controls, PCOS cases were younger (median age, 29.0 vs 36.0 years), with a higher median body mass index (discovery, 28.3 vs 23.6 kg/m^2; validation, 28.1 vs 23.7 kg/m^2) and higher median AMH level (discovery, 6.13 vs 1.59 ng/ml; validation, 6.32 vs 1.58 ng/ml). Good correlation was observed between AMH and AFC in the discovery and validation cohorts, with Spearman correlation coefficients of 0.84 and 0.85, respectively. A serum AMH cut-off of 3.2 ng/ml (23 pmol/l) was determined in the discovery cohort, which achieved 86.2% sensitivity and 86.1% specificity. In the validation cohort, this cut-off achieved 88.6% (95% confidence interval [CI] 85.3–91.3) sensitivity and 84.6% (95% CI 81.1–87.7) specificity, with an AUC of 93.6% (95% CI 92.2–95.1). In women aged≤35 years, the AMH cut-off of 3.2 ng/ml showed 88.5% (95% CI 86.2–90.5) sensitivity and 80.3% (95% CI 76.6–83.6) specificity; in women aged >35 years, specificity remained high (90.1%; 95% CI 87.3–92.5) but sensitivity was lower (77.8%; 95% CI 66.4–86.7). The Elecsys AMH Plus immunoassay provides a robust method for identifying PCOM as part of PCOS diagnosis with a cut-off of 3.2 ng/mL (23 pmol/l).

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AEP784

Polycystic ovary syndrome is burdened with a high comorbidity rate and medication use independent of BMI: A longitudinal community based study

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Objective
To investigate comorbidity rate, symptoms, overall morbidity, medication useand use of health care services among women with polycystic ovary syndrome (PCOS).
Design
Community-based prospective cohort study.
Patients
Womenreporting oligo/amenorrhea and hirsutism at age 31 and/or PCOS diagnosis by age 46 (n=280) and controls without PCOS related symptoms or diagnosis (n=1573) in the Northern Finland Birth Cohort 1966.
Main outcome measures
Self-reported diseases and symptoms diagnosed by a doctor, overall morbidity score calculated from the self-reported diagnoses, medication and supplement use and use of health care services at ages 31 and 46.
Results
The overall morbidity was increased in women with PCOS as they reported having higher occurrence of diagnosed diseases both at age 31 and 46 years. Moreover, the overall medication use was higher among affected, especially before adjustment with BMI. Women with PCOS had a higher risk for diagnosed disease at both ages [31: RR (95% CI): 1.19 (1.02 – 1.39) and 46: RR: 1.29 (1.11 – 1.50)]. Diseases more prevalent in PCOS even after adjustments both at age 31 and 46 were gastric/duodenal ulcer [OR (95% CI): 2.79 (1.02 – 7.64) and 2.12 (1.01 – 4.45), respectively], migraine [1.50 (1.05 – 2.14) and 1.58 (1.17 -2.13)] and fractures [1.63 (1.13 – 2.36) and 1.73 (1.24 – 2.41)].By age 31, women with PCOS had a higher prevalence of repeated respiratory infections, emphysema/chronic bronchitis, gynecological infections, cancer and other sickness or injury compared to control women. Furthermore, by age 46, women with PCOS had a higher prevalence of hypertension, type 2 diabetes mellitus, hypothyroidism, hyperthyroidism, salpingo-oophoritis, depression, tendinitis as well as knee, back and shoulderosteoarthritis, fibromyalgia, pre-eclampsia and endometriosis. As for infections, the women reported having more often recurrent infections, pneumonias, recurrent otitis, common colds and higher susceptibility to infections than other women. In addition, women with PCOS reported more often symptoms related to autoimmune diseases. Interestingly, use of health care services did not differbetweenthe groups either at age 31 nor 46. All results were adjusted for BMI, alcohol consumption, smoking, physical activity, education and marital status.
Conclusion
Women with PCOS are burdened with extensive comorbidity up till late fertile age independent of BMI, although higher BMI aggravates the risk for medication usage. Identification of the women with the syndrome as well as early preventive actions should be considered to alleviate health risks related to the syndrome.

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AEP785

Structural analysis of the impact of a novel androgen receptor gene mutation in two adult patients with mild androgen insensitivity syndrome

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Context
Androgen insensitivity syndrome (AIS) is a rare X-linked recessive disordercaused by mutations in the androgen receptor (*AR*) gene resulting in variable target tissue resistance to androgen action. The underlying molecular defect causes a spectrum of androgen dysfunction ranging from gynecomastia and/or infertility in mild AIS (MAIS) to variable degrees of ambiguous or undermasculinized genitalia in partial AIS to complete testicular feminization in complete AIS. To date, more than 800 different mutations in the*AR* gene have been identified.
Objective
We report a previously undescribed mutation in the *AR* gene associated with MAIS in two adult patients, one presenting for infertility and the other for a decrease in athletic performance. We characterize the functional impact of this mutation using 3D modeling studies.
Patients
Patient 1 was referred at the age of 38 years for infertility. He had gynecomastia and normal external genitaliaexcept for mild hypospadias. His semen analysis showed oligoasthenoteratospermia. Lab results revealed high testosterone levels, an elevated FSH, and an elevated androgen sensitivity index (ASI) suggesting AIS. The couple underwent successful *in vitro* fertilization and intracytoplasmic sperm injection resulting in a twin pregnancy. Patient 2 was referred at the age of 45 years for evaluation of a fatigue and a decrease in physical athletic performance. He had a history of gynecomastia, surgically treated during adolescencebut normal external genitalia. He alsopresented with oligoasthenoteratospermia, hightestosterone plasma levels and an elevated ASI. Despite his impairedsemen analysis, he fathered two children without assisted reproductive technology. Because of his persistent fatigue, the patient was offered a trial of high dose dihydrotestosterone therapy which improved his symptoms and his quality of life. Family history for infertility or gynecomastia was negative in both patients.
Results and conclusions
Sequence analysis of *AR* gene in the two patients revealed a common previously undescribed missense mutation, *Ala699Thr*, within the ligand binding domain. Structural analysis showed that this mutation may impact dimer stability upon ligand binding or may affect allosteric changes upon dimerization. This study highlights the usefulness of structural studies in providing a greater understanding of the functional consequences of a mutation and expands the databaseof *AR* gene mutations. The proper diagnosis of adult patients with MAIS may be helpful for the adequate counseling of infertile male patient undergoing assisted reproductive techniques. In addition, a trial of high dose androgen therapy may improve symptoms of hypogonadism in patients with MAIS.

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AEP786

Endogenous doping: Physical exercise acutely increases testosterone levels. Results from a meta-analysis

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Background
Physical exercise represents the first-line therapy in the management of metabolic diseases, considering its beneficial properties on blood pressure, glyco-lipid profile, body composition and hormonal imbalances. On the other hand, testosterone is largely investigated in the setting of competitive sport, representing the main doping source. Although endogenous testosterone levels are demonstrated to be affected by both acute exercise and resistance training, the dynamic regulation of androgen production after physical activity is still a matter of debate.
Aim of the study
This meta-analysis was designed to assess whether physical exercise acutely affects testosterone levels in men.
Methods
The literature search was conducted to identify longitudinal trials evaluating the acute change of testosterone levels after physical activity in adult men published in English language until October 2019 (PROSPERO registration

ID: 157348). Data were extracted using testosterone levels before and after exercise as primary endpoint, considering sex hormone binding globulin (SHBG) and free testosterone (fT) as secondary endpoints. Sensitivity analyses were performed considering the sample collected (i.e. blood or saliva), the intensity of the physical exercise (mild, moderate or high, considering either the intensity reported in the manuscript or the percentage of the maximal exercise intensity described), and the interval between the end of the exercise and the sample collection (0–2 minutes, 3–30 minutes, and 31–60 minutes after the activity).
Results
Forty-eight studies were included in the analysis, accounting for 126 trials. A total of 569 patients were enrolled (mean age 29.7 + 13.1 years).The physical activity increased acutely total testosterone levels, considering both serum and saliva samples ($P < 0.001$, respectively). In particular, testosterone levels significantly increased after moderate ($P < 0.001$) and high intensity ($P < 0.001$) exercises, but not after mild physical activity ($P = 0.190$). Moreover, the testosterone increase was evident when measured immediately at the end of the exercise and within 30 minutes ($P < 0.001$), but not after 30 minutes ($P = 0.930$). Similar significant results were obtained considering fT, while SHBG did not change after physical activity ($P = 0.090$).
Conclusion
Albeit considering the high heterogeneity of included studies, the comprehensive evaluation of the acute physical activity effect on testosterone levels identified a clear increase after exercise, irrespective of the sample collected. The main determinant of this fluctuation was the exercise intensity, with a mechanism that seems to be mostly SHBG-independent. In particular, moderate/intense physical activity resulted able to increase endogenous androgenic production, albeit acutely and transitory.

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AEP787

Clinical and genetic characterization of two cases of central hypogonadism in Klinefelter syndrome

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Introduction
Klinefelter syndrome (KS) is generally characterized by late adolescence/young adulthood onset of primary hypergonadotropic hypogonadism. Fourteen cases have been previously reported on apparently unexplained isolated hypogonadotropic hypogonadism (IHH) in KS. Gonadotropins defect was variably associated with anosmia or other pituitary hormones deficiencies, but no cause could be clearly identified to explain the central defect. We describe the clinical and genetic features of two additional cases followed up at two clinics in Northern Italy.
Case 1
A 60-year-old Caucasian man was referred for genital infantilism and smell defect, for which he had never sought medical attention before. He had a family history of infertility and anosmia; his parents were unrelated. His past medical history included recurrent respiratory infections resulting in restrictive ventilatory defect. The patient reported he had not gone through puberty during adolescence, and eunuchoid body proportions and infantile penis were observed at physical examination. Scrotal ultrasound revealed testes hypotrophy (volume <1 ml). Cytogenetic analysis documented 47,XXY karyotype. Nevertheless, IHH was found on hormonal assessment (total testosterone 1.0 nmol/l, LH 0.1 mIU/ml, FSH 0.1 mIU/ml), while other pituitary hormones were normal.
Case 2
A Caucasian boy with prenatal diagnosis of mosaic KS (47,XXY)(46,XY) confirmed after birth,presented at 17 years of age with small and firm testes (right 6 ml, left 8 ml) and first grade obesity. As a child, he had suffered from dyslexia and incomplete pubertal development. At 20 years of age hormonal exams were obtained and unexpected results consistent with IHHwere found (total testosterone 3.7 nmol/l, LH 3.5 mIU/ml, FSH 2.3 mIU/ml), while other pituitary hormones were preserved. Smell identification test was normal and the patient had no family history of anosmia or infertility.
Diagnostic work-up
Iron overload was excluded in both patients. Sellar region was normal on magnetic resonance scans. Finally, genetic analysis performed by next generation sequencing of IHH associated genes was negative in both patients.
Conclusion
Unexplained central hypogonadism rarely occurs in KS. The mechanism by which the gonadotropin defect is determined in these patients is unknown; coexistence of KS and normosmic isolated hypogonadotropic hypogonadism or Kallmann syndrome could be possible; alternatively,chronic metabolic or systemic comorbidities may suppress the hypothalamus-pituitary-testis axis in some KS subjects resulting in central hypogonadism; finally, these patients may represent a rare variant of KS with more extensive endocrine involvement besides the testicular defect.

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AEP788

Clinical and genetic overlap between congenital hypogonadotropic hypogonadism and cornelia de lange syndrome

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Background
Congenital hypogonadotropic hypogonadism (CHH), a clinically and genetic heterogenous sydrome, is caused by >40 known loci whose mutations share the ability to cause defects in the ontogeny of the GnRH neuron network leading to absent/incomplete puberty and infertility. Cornelia de Lange Syndrome (CdLS) is similarly heterogenous disorder (distinctive facies, psychomotor delay, growth retardation and upper limb malformation) caused by mutations in 7 different genes in the cohension complex with a subset who share CHH phenotypes including cryptorchidism, micropenis, and/or delayed puberty, suggesting hypogonadism, although formal endocrine evaluation is lacking.
Methods
Given thephenotypic overlap between these syndromes, exome sequencing was performed in probands with clinical features of both CHH and CdLS or CHH alone, focusing specifically on pathogenic variants in known 7 CdLS genes (*SMC3, NIPBL, SMC1A, RAD21, HDAC8, BRD4* and *ANKRD11*). *In vitro* assays were performed on identified mutants and GnRH3:GFP zebrafish were used to explore the pathogenic role of *SMC3* and *NIPBL* in GnRH neuron development.
Results
Exome sequencing revealed rare sequencing variants (RSV) in *NIPBL* (p.P2761Cfs*4, p.R2298C) and a *de novo* missense RSV in *SMC3* (p.C549Y) in 3 patients exhibiting CHH and CdLS, all of which were absent in gnomAD controls.*NIPBL*p.R2298C has previously been reported in CdLS patients and is considered to be pathogenic. *NIPBL*p.P2761Cfs*4may escape nonsense-mediated decay, thus leading to a truncated NIBPL protein that lacksits 39 N-terminal amino acids. SMC3 C549 residue is located in the hinge domain of SMC3, and C549Y enhances the hinge binding to SMC1 *in vitro*. We also identified two novel protein truncating variants in *NIPBL* (p.E2656*& p.E2696Sfs*6) in different CHH patients without a CdLS diagnosis. Both *Nipbl* and *Smc3* are highly expressed along the migratory path of GnRH neurons from the nasal placode to the hypothalamus. Knock down of *Smc3* and *Nipbl* in GnRH3:GFP zebrafish reduced GnRH neuron numbers, indicating their implication in GnRH neuron biology.
Conclusion
Novel pathogenic variants in cohesion genes (*NIPBL* and *SMC3*) underly CHH with or without CdLS implicating the cohesion complex in GnRH neuron biology. Transcriptomic and DNA accessibility (ATAC-seq) studies in zebrafish and fibroblasts from the *SMC3*-mutated patient are underway to further explore the common mechanism of these two rare developmental diseases.

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AEP789

X-Linked Adrenoleukodystrophy: Report of an atypical case

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Introduction
X-linked adrenoleukodystrophy (X-ALD) is caused by a mutation in the ABCD1 gene, which encodes for a peroxisomal very long chain fatty acid (VLCFA) transporter. Clinically, X-ALD can present a wide spectrum of phenotypes, being the most frequent Adrenomyeloneuropathy, with ataxia, spastic paraparesis, sexual and sphincter dysfunction. Adrenocortical insufficiency (AI) occurs mainly in paediatric age and it can be the first manifestation of the disease in some cases.
Case report
44 year old male, with AI diagnosed at 6 years old, was referred to an endocrinology consultation. He was under hydrocortisone (HC) 20 mg+10 mg and fludrocortisone (FC) 0.1 mg od. He also mentioned complains of dizziness, gait disturbance and erectile dysfunction in the past 6 months and underwent a brain MRI (July 2015) that showed "T2 hyperintensity of internal capsule, cerebral peduncles, pons and medulla oblongata… suggestive of amyotrophic lateral sclerosis". Blood tests revealed ACTH 124 pg/ml (9–52), cortisol 27µg/dl (5-25), renin 93 µU/ml (7–76) and 21–hydroxylase antibodies 0.74 U/ml (< 1.0); other autoimmune markers were negative. Serum VLCFA were elevated and genetic test revealed a mutation in ABCD1 gene (c.1817C>T – p.S606L). One year after diagnosis, he was under HC 35 mg/day and FC 0.1 mg/day; he had grade 4 spastic paraparesis, sexual and sphincter dysfunction and he was under a rehabilitation programme. In April 2018, he had dysarthria, difficulties in fine motor skills, need for a walking aid and memory and concentration impairment. After 4 months, he had a rapid worsening of the general condition, with cognitive decline, poor understanding of speech and hearing loss. MRI (November 2018) revealed alterations typical of different phases of X-ALD, with current inflammatory activity. He was submitted to high-dose corticotherapy, with modest improvement of motor skills. In July 2019, he was admitted to the Emergency Department due to adrenal crisis, pneumonia and seizure; he was hypotensive and febrile; blood tests showed hyponatremia and hyperkalaemia; he needed non-invasive ventilation for 3 days. He was treated with ceftriaxone and azithromycin, with improvement. He was discharged to a long-term care unit. On last follow-up consultation in December 2019, he was totally dependent and aphasic; he was under HC 40 mg/day and FC 0.1 mg/day. His blood tests were normal.
Conclusion
This case demonstrates that in X-ALD, adrenocortical insufficiency can precede neurologic symptoms more than 3 decades. As was the case of this patient, clinical phenotypes of are not static. X-ALD must be considered in male patients with AI, especially if autoimmune markers are negative.

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AEP790

Clinical evaluation and genetic analysis of patients affected by premature ovarian insufficiency: Identification and characterization of a new mutation of the BMP-15

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Background
Premature ovarian insufficiency (POI) is an ovarian defect characterized from primary or secondaryamenorrhea, high levels of FSH (> 25 UI/l) and low levels of estrogen, which occurs before age 40.
Objective
The aim of the study was to evaluate the clinical features and genetic causes of a group of 68 patients with POI.
Methods
We performed anamnestic and clinical evaluation, hormonal and autoimmunity assessment, pelvic ultrasonography, bone densitometry (DXA) and genetic analysis in 68 women presenting with POI. Genetic analysis was performed for the research of FMR1 pre-mutation and mutations of genes involved in BMP-15 and GDF-9 folliculogenesis. DNA was extracted from peripheral white blood cells. All the exons of the BMP-15 and GDF-9 genes were amplified by polymerase chain reaction and subjected to direct sequencing. A novel heterozygous mutation in exon 2 of BMP-15 gene was identified in a patient. Functional studies were performed to assess the in vitro effect of the identified BMP-15 gene variant. For the functional study COV434 cells of ovarian granulosa were used, which consistently express BMP responsive element (BRE) by assay with luciferase.
Results
63 patients presented secondary amenorrhea, 5 primary amenorrhea. Mean age of menopause was 28 years. 9 patients (13%) had a family history of POI, 28 patients (41%) had one or more autoimmune diseases associated with POI. Pelvic ultrasound revealed the absence of ovarian follicles in 19 patients. Bone densitometry appeared dramatically reduced in 2 women. In 5 patients (7%) FMR1 pre-mutation was detected. In 1 patient we identified a new pathogenetic mutation in heterozygosis c.406G> C (V136L) of BMP-15. We found no mutations in the GDF-9 gene. After transfection in COV434 BMP-15 cells mutated V136L has a significantly reduced activity both if transfected by itself and along with the wild type gene.
Conclusion
POI is a multifactorial pathology with general health implications on affected women. Autoimmunity, familiar and genetic causes represent the most common etiology. We identified FMR1 pre-mutation in 7% of the women and a new BMP-15 mutation responsible for the observed phenotype.

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AEP791

A case of Swyer syndrome with successful extirpation of gonadal tissues in 70 years old women

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A 27 year old woman was examined in 1977 because of amenorrhea andhirsutism. Hormonal evaluation revealed elevated levels of gonadotrophins simoultaneously with biochemical and clinical hyperandrogenism. Cytogenetic evaluation confirmed presence of male karyotype (46XY) and Swyer syndrome (pure gonadal dysgenesis) was diagnosed. Patient underwent laparotomy, however no gonadal tissue was found during this procedure. A few years later molecular genetic evaluation demonstrated presence of Y sequencies PABY, SRY from the short arm of Y chromosome, DYZ3 sequencies from the centromeric region and sequencies SY85, SY132, SY156, DYZ1 from the long arm of Y chromosome. Patient did not visit endocrinologists for many years. She was treated by psychiatrists because of depression. In her 70-ties (2019) she was admitted to the hospital because ofabdominal pain. Imaging methods and physical examination did not confirman acute abdomen, but MRI demonstrated presence of testicular tissue and crurapenis in the pelvic region. Patient underwent laparoscopic surgery with exstirpation of gonads(testes, epididymis, d. epididymidis) and crura penis. Few months after surgery a marked regression of hirsutism, decrease in serum testosterone levels and marked improvement of depression was observed.
Conclusion
Swyer syndrome is a rare disease with a high risk of malignant transformation of residual gonadal tissue. This case study reports an unusual course of disease, where after 70 years we did not register malignant overthrow of gonads and their surgical extirpation has led to improvement of hyperandrogenism and quality of life.

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AEP792

Ovarian mucinous cystadenoma presenting with virilization

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Background
Ovarian mucinous cystadenomas are classically considered as 'non-functional' tumors. Cystadenomas are among the most common benign ovarian neoplasms. Compared with serous cystadenomas, mucinous cystadenomas occur less frequently, are more often unilateral and can attain an enormous size. Most of these tumors are asymptomatic and found incidentally on pelvic examination or with ultrasound. We present an unusual case of a mucinous cystadenoma presenting with severe virilization in a 71-year old woman.
Case
A 71-year old female was referred to our out-patient endocrinology clinic because of rapid progressive androgenic alopecia, clitoromegaly and male pattern pubic hair growth since one year. Her medical history was unremarkable. Serum level of testosterone was 3.35 µg/l (normal range < 0.4 µg/l) and the dihydroepiandrosterone sulfate (DHEAS) level was 267 µg/l (normal range 100–800 µg/l). Magnetic resonance imaging of the abdomen revealed a 5.5 × 3 × 3 cm cystic ovarian mass. A bilateral salpingo-oophorectomy was performed without complications. Histopathology showed an unilocular cystic structure with a yellowish content and compatible with a mucinous cystadenoma. Postoperative testosteron levels quickly normalised (< 0.4 µg/l).
Discussion
Rapidly developing postmenopausal hyperandrogenism easily turns into a diagnostic challenge for the clinician. Most cases result from adrenal or ovarian tumors but atypical causes must be recognized as well. To date and to the best of our knowledge there are only five cases of mucinous adenoma causing virilization in postmenopausal women identified in the literature. This sixth case adds strength to the link between ovarian mucinous cystadenoma and severe, rapidly progressive hyperandrogenism during menopause. In this case surgical resection is the treatment of choice.

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AEP793

Bone mineral density in prepubertal and pubertal children with turner syndrome

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Aim
To evaluate bone mineral density (BMD) in children with different karyotype variants of Turner syndrome (TS) depending on the stage and the onset of puberty (spontaneous or induced).
Methods
The total studied group consisted of 75 children with TS from 8 to 17 years (mean age 14.2±2.61), who were regularly followed-up in the University hospital (Minsk) and age matched 25 healthy controls. TS was diagnosed according to the results of karyotyping at the age of 8.2±5.16 years. 22 patients were in prepuberty (mean age 11.4±2.1 years). 53 girls had II-V stage of puberty according to Tanner (mean age 15.26±1.95 years). Spontaneous onset of puberty was observed in 14 girls aged 12.07±1.66 years. 39 patients underwent puberty initiation (the age for starting estrogen replacement therapy was 13.27±1.26 years). Depending on the karyotype, 3 groups of patients were identified: group 1 - with karyotype 45,X (n=42), group 2 - with mosaic karyotype 45,X/46,XX (n=9), group 3 - with structural anomalies of X chromosome (n=24). Body composition with evaluating of mineral component was made by DEXA with the calculation of lumbar spine (L_{1-4}) BMD (g/cm^2) and Z-test.
Results
54.5% of prepubertal patients with TS revealed low BMD of lumbar spine L_{1-4} vs 64.1% in pubertal girls. A significant increase of BMD was revealed in patients of puberty age in comparison with the group of prepubertal children (0.95 [0.85;1.02] g/cm^2 vs 0.76 [0.69;1.82] g/cm^2, P=0.0001). A statistically significant increase in the Z-test in this groups was not established (–1.25 [–1.95; –0.78] vs –1.1 [–1.7; –0.4], P=0.2). There were no differences in BMD depending on karyotype both at the prepuberty and puberty age. The BMD of the lumbar spine (L_{1-4}) was significantly lower both in patients with spontaneous puberty and in the group of girls with estrogen replacement therapy compared to the control group. In girls with TS and spontaneous puberty a low BMD was detected in 57.2% of cases (Z=–1.9±0.87), whereas in the group with stimulated puberty - in 68.4% of patients (Z=–1.8±0.62). A direct correlation of spine BMD and estrogen therapy duration (rs=0.6, P=0.0001) was found in girls with TS.
Conclusions
A significant increase in BMD without an improvement in the Z-test was found in pubertal patients with ST in contrast to prepubertal children. Decreased of BMD are more often diagnosed in patients with stimulated puberty, due to the later initiation of estrogen therapy. Long-term estrogen replacement improves BMD.

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AEP794

Investigating the impact of preoperative obesity-associated hyperandrogenemia in women and hypogonadism in men on weight loss following bariatric surgery

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Background
In severe obesity, hypogonadism in men and androgen excess in women are frequently observed. Sex hormones play an important role in body composition, glucose and lipid metabolism. Bariatric surgery is the most effective treatment strategy to combat morbid obesity. However, if preoperative gonadal dysfunction impacts weight loss and metabolic improvements after surgery is not known.
Methods
49 men and 104 women were included in a retrospective analysis. Anthropometric characteristics, glucose and lipid metabolism and androgen concentrations were assessed preoperatively and 17.9±11 or 19.3±12 months-postoperatively in men and women. Men with and without preoperative hypogonadism (HYPO vs CON_{male}), as well as women with or without preoperative hyperandrogenemia (HYPER vs CON_{female}) were compared.
Results
Inmen preoperative hypogonadism was present in 55%, linked to a higher BMI (HYPO 50±6 kg/m^2 vs CON_{male} 44±5 kg/m^2, P=0.001). Bariatric surgery results incomparablechanges in BMI in HYPO and CON_{male} (–16±6 kg/m^2 vs –14±5 kg/m^2, P=0.30) and similar improvements in glucose and lipid metabolism. Weight loss reversed hypogonadism in 93%. In women androgen excess was present in 22%, independent of preoperative BMI (CON_{female} 44±7 kg/m^2 vs HYPER45±7 kg/m^2, P=0.57). Changes in BMI and metabolic improvements were comparable in HYPER and CON_{female} (–15±6 kg/m^2 vs –15±5 kg/m^2, P=0.88)after bariatric surgery. Hyperandrogenemia was reversed in 61%.
Conclusions
Despite being frequently observed, hypogonadism in men and androgen excess in women have no impact on postsurgical improvements in body weight, glucose and lipid metabolism. Weight reduction resulted in reversal of hypogonadism in almost all men and of hyperandrogenemia in the majority of women.

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AEP795

The vulnerability of prepubertal ovarian steroidogenesis to AhR-mediated TCDD action occurs during a time-restricted window in mice

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Background
In females, timing of puberty and fertility require estradiol (E2) action at the infantile and late juvenilestages and are tightly influenced by environ-

mental cues. A regulator of intra-ovarian E2 synthesis during reproductive life is the aryl hydrocarbon receptor (AhR). However, its action on E2 synthesis and its capacity to mediate the effect of endocrine disrupting chemicals (EDC)s has not been thoroughly evaluated during the prepubertal period.
Objectives
Determining intrinsic and EDC-induced activity of AhR on E2 synthesis at critical prepubertal stages for reproductive function programming.
Methods
The intra-ovarian expression of components of the steroidogenesis pathway, prototypical AhR target genes (*Ahrr*, *Cyp1a1*) and E2 contents were examined in the *Ahr*knockout (*Ahr*$^{-/-}$) mouse at the neonatal (7 days postnatal (dpn)), infantile (14 dpn), early (21 dpn) and late juvenile stages (28 dpn) and in the highly dioxine sensitive C57Bl/6J mouse strain treated at 14 or 28 dpn with AhR ligands, FICZ and TCDD. The expression of AhR was analyzed in both mouse and human ovaries.
Results
Intrinsic AhR pathway became active only at the end of the prepubertal period, as revealed in *Ahr*$^{-/-}$ mice *versus* *Ahr*$^{+/+}$ miceby the down-regulation in the relative intra-ovarian contents of E2, *Cyp19a1* aromatase and *Ahrr*transcripts exclusivelyat 28 dpn. AhR activation by exogenous ligands could occur at any stage, as suggested by TCDD-induced *Ahrr* and *Cyp1a1* expression at both 14 and 28 dpn, but itimpaired *Cyp19a1* expression and E2 synthesis only at 28 dpn. Although AhR is detected in the ovary throughout the prepubertal period, its nuclear localization, reflecting its activity, in granulosa cells responsible for E2 synthesis, was weak at the infantile stage.
Discussion
AhR regulation of E2 synthesis would start at the approach of puberty. We propose that AhR-mediated EDC action specifically at this stage could be particularly detrimental for reproductive function programming.
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AEP796

The association between hormone replacement therapy and sarcopenia in postmenopausal women: The korea national health and nutrition examination survey, 2008–2011

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Objective
Menopausal transition contributes to sarcopenia, but the effects of hormone replacement therapy (HRT) on sarcopenia in postmenopausal women have not been determined. This study assessed the effect of HRT on sarcopenia in postmenopausal women.
Methods
The present study included 4,254 postmenopausal women who participated in the Korea National Health and Nutritional Examination Surveys in 2008–2011. Appendicular skeletal muscle mass divided by weight (ASM/Wt) and the prevalence of sarcopenia were analyzed in groups of women stratified by duration of HRT.
Results
ASM/Wt was higher and the prevalence of sarcopenia was lower in subjects with a history of prolonged (≥ 13 months) than in subjects without a history of HRT. After adjusting for multiple confounding factors, HRT remained significantly associated with estimated mean ASM/Wt and the prevalence of sarcopenia (odds ratio: 0.59; 95% confidence interval: 0.40–0.87; $P<0.01$). A multivariate model showed that ASM/Wt and the prevalence of sarcopenia were independently associated with age, history of hypertension, physical activity, age at menopause, and a history of HRT. Subgroup analysis showed that the association between duration of HRT and the prevalence of sarcopenia was maintained in younger (< 65 years old) and leaner (body mass index < 25 kg/m^2) postmenopausal women.

Table 1 Odds ratios for the prevalence of sarcopenia in postmenopausal women stratified by duration of hormone replacement therapy.

	No HRT ($n=3,656$)	HRT for 1–12 months ($n=302$)	HRT for ≥13 months ($n=275$)	*P* for trend
Unadjusted	1 (ref)	0.93 (0.68–1.27)	0.67 (0.47–0.95)*	0.08
Model 1	1 (ref)	0.95 (0.69–1.31)	0.64 (0.45–0.92)*	0.05
Model 2	1 (ref)	0.90 (0.66–1.24)	0.59 (0.40–0.87)**	0.03

Data were analyzed using complex samples logistic regression and are expressed as odds ratio (95% confidence interval).
Model 1: adjusted for age, age at menarche, age at menopause, and number of pregnancies.
Model 2: adjusted for age, age at menarche, age at menopause, number of pregnancies, past history of OC, past histories of DM and HTN, smoking history, physical activity, and energy intake (total, proteins, carbohydrates, and fats).
*$P<0.05$, **$P<0.01$.

Conclusions
The present study showed that prolonged HRT was associated with high muscle mass and a low prevalence of sarcopenia in postmenopausal women, suggesting that HRT may have a protective effect on sarcopenia in postmenopausal women.
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AEP797

Ovarian reserve and serum concentration of thyroid peroxidase antibodies in euthyroid women with different polycystic ovary syndrome phenotypes

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Objective
It has been shown that women with PCOS as well as with autoimmune thyroiditis (AIT), are characterized by increased incidence of infertility. Serum anti-Müllerian hormone (AMH), which reflects ovarian reserve, is elevated in PCOS women and is decreased in women with AIT. The Rotterdam criteria recognize four clinical PCOS phenotypes,i.e.,phenotype Acharacterized by clinical and/or biochemical hyperandrogenism (HA), menstrual dysfunction (oligo/amenorrhea) (Oligo) and polycystic ovarian morphology (PCOM), phenotype B (HA+Oligo), phenotype C (HA+PCOM) and phenotype D (Oligo+PCOM). To date, there is no study evaluating ovarian reserve and TPOAbs in different PCOS phenotypes. The aim of the present study was to investigate the relation between serum concentrations of TPOAbs and ovarian reserve in different PCOS phenotypes.
Patients and methods
We examined 141 women with PCOS (phenotype A was diagnosed in 67 (47.5%) women, phenotype B in 30 (21.3%), phenotype C in 28 (19.9%), phenotype Din 16 (11.3%)) and 88 control subjects of similar age ($P>0.05$). Physical examination was performed in all women. Serum concentration of LH, FSH, estradiol, total testosterone, AMH, TSH, thyroid hormones and TPOAbs were assessed and ultrasound of the ovaries was performed.
Results
Serum concentrations of TSH, fT4 and fT3 did not differ between the studied groups (all $P>0.05$), all women were euthyroid. We observed positive serum TPOAbs in 31 (21.9%) women with PCOS and in 21 (23.9%) controls ($P=0.07$). We did not observe differences in frequency of detection of positive serum TPOAbs between phenotype A (15 women, 22.4%), phenotype B (5 women, 16.7%), phenotype C (10 women, 35.7%) and control group (21 women, 23.9%) ($P>0.05$). Interestingly, only one woman had positive serum TPOAbs (6.3%) in phenotype D. Serum AMH concentration was markedly higher in thewhole PCOS group ($P<0.01$) and in phenotype A ($P<0.01$) vs controls when serum concentration of TPOAbs was negative. However, in the groups with positive serum levels of TPOAbs, serum concentration of AMH did not differ between PCOS phenotypes and controls (all $P>0.05$). We foundrelationships between serum TPOAbs concentrations and hip circumference ($P=0.03$) and serum concentration of estradiol in the whole group ($P=0.002$).
Conclusions
Frequency of serum detection of positive TPOAbs did not differ between PCOS phenotypeswith clinical/biochemical hyperandrogenism and control group, however, phenotype D is characterized by the lowest frequency of occurrence of positive TPOAbs. We observed differences in ovarian reserve between PCOS and control group with negative TPOAbs, whereas presence of TPOAbsabolished this differences.
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AEP798

Comparison of three automated assays of AMH

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Anti-Mullerian Hormone (AMH) is a 140 kDa gonadal glycoprotein of the TGFβ family, with two subunits linked by two disulfide bridges. Since a first assay in 1990, three generations of assays occurred: the 1st and 2nd were manual assays. The 3rd was automated: Access AMH Kits (Beckman Coulter) and Elecsys AMH (Roche). We had the opportunity to compare two new analysers with the Elecsys AMH: Vidas (Biomérieux) and Lumipulse G (Fujirebio). The later are one-step sandwich immunoenzymatic (fluorescence detection) and two-step sandwich chemiluminescence, respectively. The population studied consisted of 50 women of reproductive age (27 [20.5–37.7] yr, median [5th-95th] percentiles; BMI 21.7 [18.2–29.1] kg/m²). The sera collected were centrifuged, aliquoted in 3 aliquots and frozen until the day of the assay. Intra-laboratory precisions reported by the suppliers were: CV < 2.1% for sample panels with concentrations from 0.41 to 22.44 ng/ml for the Lumipulse and CV < 10.6% for sample panels with concentrations from 0.22 to 7.37 ng/ml for the Vidas. The results obtained were closely correlated with no significant deviation from linearity (Passing Bablok test): Elecsys vs Vidas correlation coefficient $r = 0.976$, [Elecsys] = 0.0778767 + 1.086758*[Vidas] ng/ml & Elecsys vs Lumipulse $r = 0.913$, [Lumipulse] = 0.0308871 + 1.097997*[Vidas] ng/ml. On the Bland-Altman graphs, 3 outliers were found outside the concordance limits for the Vidas against 1 outlier for the Lumipulse. Despite these very good correlations and minor biases, an important problem rests with the proposed reference values which are not similar. For instance, for a 30-34 yr old woman: Elecsys 2.81 [0.71–7.59], Lumipulse 1.557 [0.065–10.042], Vidas 3.55 [1.19–7.00] ng/ml. A combination of reasons may explain this. Firstly, an international AMH standard is not yet used for theses assays. Furthermore, AMH concentrations can be influenced by different factors (ethnicity, tobacco, oral contraceptives, etc.). Reference values may thus be different from so-called normal values in healthy subjects. Specifics about the determination of reference ranges by the manufacturers are then critical (Ferguson, Reprod Biomed Online, 2018). Indeed, precise identification of these ranges is mandatory to assess the usefulness of determining AMH concentration with any apparatus.

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AEP799

Investigation of the mechanism of action of duodenal mucosal resurfacing in insulin resistant women with polycystic ovarian syndrome. the DOMINO multicentre randomised controlled trial

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Introduction
Duodenal mucosal resurfacing (DMR) is a novel therapy for T2DM. It involves the hydrothermal ablation of up to 14 cm of the duodenal mucosa through a specially designed endoscopic catheter. The procedure is performed under general anaesthesia, patients are discharged the same day and it does not involve the implantation of a foreign body. Cohort studies have demonstrated that DMR induces meaningful hbA1c reductions of 0.9–1.4% by 3 months that are largely maintained at 12 months without significant weight loss. This weight loss-independent effect on glycaemia remains elusive. Herein, we sought to investigate the effect of DMR on insulin sensitivity and menstruation of euglycaemic patients with PCOS and insulin resistance.

Methods
In this first of its kind, double-blinded RCT with a 24 week follow-up, thirty insulin resistant PCOS women were randomised at 1:1 to either DMR or sham endoscopy. Diagnosis of PCOS was based on NIH criteria. Specialist lifestyle modification was delivered to all patients. All patients underwent OGTT to measure insulin secretion and the gold standard euglycaemic hyperinsulinaemic clamps with stable isotopes to measure insulin sensitivity, at baseline, 2 weeks and 3 months after intervention.
Results

Baseline clinical characteristics

	DMR ($n = 15$)	Sham ($n = 15$)
Age (years)	30.60 ± 5.22	31.60 ± 6.94
Weight (kg)	107.76 ± 18.96	121.24 ± 12.58
BMI (kg/m²)	40.20 ± 6.63	44.71 ± 3.35
Body fat (%)	43.94 ± 3.47	46.08 ± 2.05
W/H ratio	0.87 ± 0.06	0.87 ± 0.09
Glycaemic profile		
HbA1c (mmol/mol)	39.67 ± 3.74	37.67 ± 5.33
Fasting glucose(mmol/l)	5.55 ± 0.67	5.05 ± 0.59
Fasting insulin (mIU/l)	21.99 ± 8.43	27.69 ± 13.86
HOMA-IR	6.20 ± 3.38	6.15 ± 2.93

Primary Endpoints

	DMR ($n = 15$)	Sham ($n = 15$)	*P*-value
Change in total insulin sensitivity at 12 weeks (mg/kg/min)	0.14 ± 0.97	0.24 ± 1.74	0.367
Change in insulin sensitivity by HOMA-IR at 24 weeks	-0.39 ± 1.87	-1.19 ± 4.23	0.301
Number of menses in 24 weeks	3.00 [0.00, 5.00]	2.00 [1.00, 5.00]	0.434

Conclusion
DMR didn't increase insulin sensitivity in insulin resistant women with PCOS and obesity in this trial. Thus, selecting the duodenal mucosa as a therapeutic target may only be effective in T2DM but not in euglycaemic insulin resistant states. Future studies could examine the effect of DMR on insulin sensitivity in people with T2DM. Our results are likely limited by a relatively small sample size and short duration of follow-up compared to studies done in patients with T2DM.

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AEP800

Early decreases in testosterone levels in healthy adult men: A longitudinal analysis.

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Introduction
Although it is well-known that serum testosterone (T) levels decrease in ageing men, to this date no longitudinal data are available on changes in T levels in healthy young adult men.

Objective
To investigate age-related longitudinal changes in serum levels of total T, free T and sex hormone binding globulin (SHBG) in healthy young men.
Methods
Data from 999 healthy men aged 24–46years who participated in a longitudinal population-based sibling-pair study were included. After a mean follow up of 11.6±1.9 (range 7–18) years, 709 participants were re-evaluated. SHBG, luteinizing hormone (LH) and follicle stimulating hormone (FSH) were measured using Roche e801 immuno-assays. T was measured using LC-MS/MS, free fractions and body mass index (BMI) were calculated. Linear mixed effects modelling was used for longitudinal analysis. Age at baseline and BMI were used as covariates.
Results
Men were 34.5±5.5 years at baseline and 46.4±5.8 years at follow up. During this period BMI increased from 25.1 kg/m² to 26.3 kg/m². At both time points, age and BMI negatively associated with total T and free T (all $P<0.001$), and BMI also negatively associated with SHBG ($P<0.001$). During follow up, total T levels decreased 14.4% (586.51 ng/dl vs 502.22 ng/dl at baseline and follow-up, respectively, after correction for age at baseline; $P<0.001$). The decrease in total T was less pronounced after correction for BMI and changes therein with a decrease of 10.2% ($P<0.001$). Free T decreased 17.9% (11.12 ng/dl vs 9.18 ng/dl after correction for age at baseline). The decrease in free T was less pronounced after correction for BMI and changes therein with a decrease of 16.1% ($P<0.001$). After adjustment for age and BMI, SHBG increased 5.9% (37.8 nmol/l vs 40.15 nmol/l) , LH increased 6.8% (4.465 U/l vs 4.791 U/l) and FSH increased 15.5% (4.340 U/l vs 5.139 U/l) (all$P<0.001$) during follow-up. Further, older age at baseline was associated with larger changes in SHBG ($r=0.115$; $P=0.002$) and FSH ($r=0.08$; $P=0.032$).
Conclusion
Already from the 4th decade of life, healthy men experience decreases in total and free T levels, independently from changes in BMI. Given the concurrent rise in gonadotropin levels, the decline in T in our population mostly likely arises from primary testicular dysfunction. Changes in T levels were independent from baseline age, suggesting a similar linear decrease across age within our population.

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AEP801

11-Ketotestosterone is the Predominant Androgen in Castration Resistant Prostate Cancer

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Background
The treatment of metastatic castration-resistant prostate cancer (CRPC) remains dependent on Androgen Receptor (AR) mediated signalling, thus understanding all components involved in testosterone signalling in these men is of utmost importance. Recent studies have identified 11-ketotestosterone (11 KT) as a potent androgen receptor (AR) agonist present in humans. However, it is unknown if 11 KT is present at physiologically relevant concentrations in CRPC patients. In this study, we investigated the steroid hormone metabolomes of CRPC patients at baseline, during treatment with second-line therapies and after clinical progression.
Method
Plasma samples of 29 CRPC patients starting treatment with antiandrogens ($n=10$) docetaxel+prednisone ($n=10$) or cabazitaxel+prednisone ($n=14$) were selected. Five patients completed two treatments. Steroids were extracted from plasma by liquid-liquid extraction method, followed by multi-steroid profiling liquid chromatography-tandem mass spectrometry (LC-MS/MS) targeting 16 steroid hormones as well as prednisone, prednisolone and dexamethasone. Next-generation sequencing and RNAseq were performed on the tumour biopsy samples of these patients obtained at baseline ($n=20$).
Results
11 KT was the most abundant androgen in CRPC patients at baseline, with a median concentration of 0.33 nM (0.03–2.39 nM) which constituted 65.5% (43–79.1%) of the total androgen (TA) pool. Testosterone (0.13 nM; 0.03–0.64 nM) constituted 23.8% (IQR 15.0–32.3%) of the TA pool. Treatment with glucocorticoids reduced circulating 11 KT by 83.6% (IQR: 38.6–89.3%) and testosterone by 67.9% (IQR: 38.3%–79.3%) as well as 11-oxygenated androgen precursor steroids by >80%. Differential gene expression was observed between tumour biopsy samples of patients with high (>median) versus low (<median) TA concentrations. High TA concentrations at baseline were associated with longer progression-free survival ($P<0.05$).
Conclusions
This study has identified 11-ketotestosterone, a potent AR agonist, as the major circulating androgen in CRPC patients and its abundance correlates with gene expression in the tumour tissue. Thus androgen abundance in CRPC haspreviously been underestimated and routine quantification of testosterone alone may not accurately reflect the TA abundance in patients. Suppression of 11 KT and testosterone was achieved by glucocorticoid treatment, which may explain the beneficial effects of glucocorticoid treatment in CRPC patients.

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AEP802

Pituitary response to GnRH stimulation in patients with secondary hypogonadism is modulated by different FSHB -211 G/T genotypes

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Background
The *FSHB* –211 G>T single nucleotide polymorphism (SNP) is known to affect pituitary FSH output by reducing the transcriptional activity of FSHB. Identifying the response of the pituitary to exogenous GnRH stimulation in subjects with *FSHB* -211 G>T SNP could provide useful information concerning the mechanisms regulating FSH synthesis and release.
Objectives
This study aimed to assess the pituitary response to a standardized GnRH stimulation test in patients with secondary hypogonadism (SH) according to the different *FSHB* -211 G/T genotypes (GG/GT/TT).
Materials and methods
67 male patients receiving a GnRH stimulation test (0.1 mg intravenously, sampling at 2 time-points after administration) during clinical workup for SH between January 1997 and October 2018 were retrospectively selected in our university-based referral centre. Linear longitudinal mixed-effect models were used to assess the effects of SNP genotype on FSH and LH levels over time via additive and recessive models.
Results
A marked increase in serum FSH and LH following administration of GnRH with a statistically significant linear trend was found ($P<0.0001$ for both models). In both the additive and recessive models, the main effect of T allele(s) did not reach statistical significance concerning changes of FSH levels ($P=0.9473$ and $P=0.9467$, respectively), albeit interaction effects over time were significant ($P=0.0219$ and $P=0.0276$). Main and interaction effects on LH-surge were significant in both the additive ($P=0.029$ and $P=0.0013$) and recessive model ($P=0.0033$ and $P=0.0016$). The peak of serum LH levels was significantly higher in TT carriers than in GT and GG carriers ($P=0.012$)
Discussion and conclusions
The promoter polymorphism *FSHB* -211 G>T affects the pituitary response to exogenous GnRH stimulation by reducing FSH and, surprisingly, increasing LH outputs in patients with secondary hypogonadism.
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AEP803

TU score: A new proposal for an ultrasound scoring system to predict testicular function

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Background
Testicular ultrasound (US) is routinely employed in the evaluation of reproductive and sexual function. However, its use for characteristics other than testicular volume is hampered by a lack of information on the prognostic value of its findings, that to date have only been incorporated in a score proposed by Lenz *et al.* in 1993.
Objectives
We sought to explore whether testicular US examination can predict spermatogenesis and provide information on testicular endocrine function.
Materials and methods
We retrospectively reviewed 6210 testicular US examinations, finally selecting examinations from 2230 unique men after exclusion of individuals younger than 17 years of age and those affected by congenital disorders known to affect the testes. The following variables were considered: bitesticular volume (BTV), echotexture, echogenicity and presence of microlithiasis, solid lesions and varicocele; testicular asymmetry was derived via the testicular atrophy index. Concurrent fasting hormonal data were available for 1160 men, while 979 had a semen sample available from the same day as the US exam. We defined hypogonadism as total testosterone <12 nmol/l and LH > 8.16 mIU/ml and employed a sperm synthetic index to identify impaired spermatogenesis, defined as the total number of motile spermatozoa with a normal morphology (using a cut-off of 0.625×10^6/ejaculate, derived from the 5th centiles of the WHO 2010 reference parameters (39×10^6 spermatozoa × 40% motility × 4% normal forms).
Results
Through linear and logistic regression analyses BTV and testicular echostructure were independent predictors of sperm concentration, total sperm number, total motility, normal forms and sperm synthetic index ($P<0.001$ for all), while the addition of testicular echogenicity and presence of microlithiasis contributed in predicting total testosterone and LH values. We derived a new US score, termed TU score, that can predict both impaired spermatogenesis (AUC 0.73, sensitivity 72%, specificity 61%, $P<0.001$) and hypogonadism (AUC 0.71, sensitivity 71%, specificity 53%, $P<0.001$) more accurately than the Lenz score.
Conclusions
We describe the testicular US characteristics independently associated with impaired spermatogenesis and hypogonadism and propose the TU score as a simple screening method for use in subjects referred for testicular US.

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AEP804

Effects of testosterone replacement therapy on circulating resistin levels in obese hypogonadal men

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Objective
The beneficial effects of testosterone replacement therapy (TRT) in men with hypogonadism on the body composition and metabolic parametersare well-established, but the intimate mechanisms of these effects are not fully understood. Resistin is a small protein that is involved in the regulation of glucose metabolism and is considered to be key in the development of insulin resistance and to induce proinflammatory effects. We hypothesize that TRT has an impact on the adipokine profile that mediates its positive effects on the metabolism.
Design
The aim of this pilot study was to evaluate the effects of testosterone replacement therapy (TRT) on the circulating levels of serum resistin in the study population.
Methods
A total 40 men with obesity and idiopathic hypogonadotropic hypogonadism (defined as serum testosterone concentration <12 nmol/l). Testosterone replacement therapy (TRT) with Testosterone Undecanoate (Nebido) was performed at baseline and at week 6. Serum resistin concentration was determined at baseline and at week 18 by means of ELISA.
Results
Mean age ± S.D. of the study participants was 49.4 ± 10.1 years. 50% of the subjects had type 2 diabetes mellitus. Circulating resistin was negatively associated with serum HDL concentration ($r=-0.258$, $P<0.05$), and positively with fat mass as measured by BIA ($r=0.370$, $P<0.05$). TRT has led to a statistically significant reduction in circulating serum resistin levels (8172 pg/ml vs 4816 pg/ml; paired-samples t-test $P<0.021$). This association persisted even after adjustment with potential confounders.
Conclusions
TRT in obese men with idiopathic hypogonadotropic hypogonadism has led to a significant improvement of metabolic outcomes and body composition as well as to a significant reduction in serum resistin levels. As no such data on this association has been reported in the literature thus far, further prospective studies are required to elucidate this association.

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AEP805

Hypogonadism and testis impairment in patients with amyloidosis due to Apo A-I Leu75Pro mutation

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Introduction
Amyloidosis due to Apo A-I Leu75Pro mutation is a rare form of hereditary amyloidosis with systemic involvement mainly of testicle, kidney and liver. This disease finds a wide prevalence in the province of Brescia (Northern Italy), which represents a geographic uniqueness for the spread of this amyloidosis form. Somefeatures of this disease have not yet been described.
Purpose
To describe the frequency of organ damages in this amyloidosis form and above all to define the characteristics of testicular involvement for the first time in such a wide range of cases.
Materials and methods
We have retrospectively analyzed 129 male patients >18 years of age with diagnosis of ApoA-I Leu75Pro amyloidosis. Organ involvement was assessed with scrotal ultrasound, gonadal hormone levels, glomerular filtration rate estimate and cholestasis indices evaluation.
Results
Testicular involvement is predominant with respect to liver and kidney involvement, and in younger patients it is often the first and/or only manifestation of disease. The testicle is affected in 88/129 (68.2%) of the patients and considering the younger patients (18–38 years) it turns out to be the only manifestationin 30% of cases. In older age group, gonadal involvement is associated with kidney and liver impairment in 53.3% of patients. Testicular involvement manifests itself as hypogonadism, which it is primary (reduced testosterone and increased LH)in 83% of cases. Considering also FSH-Sertoli cell axis (indirect expression of spermatogenesis function), almost all patients (96.6%) have testicular impairment of both gonadal axes. In addition, an increase in testicular volumes (>253 ml) is often found in this amyloidosis form (48.2% of cases).
Discussion
In Apo A-I Leu75 Proamyloidosis, the testicular involvement is often early and it can compromise endocrine and spermatogenic testicular function. It should be noted that ApoA-I Leu75 Pro amyloidosis manifests itself as primary testicular damage with peculiar characteristics (different from many other known forms of hypogonadism): the macroorchidism and the concomitant global involvement of testicular cell populations. Conclusions: this is the first large description of testicular involvement in this form of amyloidosis. The results of this study may have important clinical implications forearly diagnosis, screening of family membersand clinical-therapeutic follow-up of these patients.

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AEP806

Seasonal changes of serum gonadotropins and testosterone in men revealed by a large data set of real-world observations over nine years

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Background
Environmental rhythmicity seems able to affect the hypothalamic-pituitary-gonadal axis in animals to achieve reproductive advantages. However, conflicting results were obtained when assessing the environmental-dependent rhythmicity on reproductive hormone secretion in humans.
Aim of the study
This study was designed to evaluate seasonal fluctuations of the main hormones involved in the hypothalamic-pituitary-gonadal axis in men, using a big data approach.
Methods
An observational, retrospective, big data trial was carried out, including all testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) measurements performed in a single laboratory between January 2010 and January 2019, using chemiluminescent microparticle immunoassay. Subjects presenting any known factor interfering with the hypothalamic-pituitary-gonadal axis were excluded from the analyses. However, according to the big data approach, no information about subjects' clinical history was available, but only the diagnostic reason for biochemical examinations. The trend and seasonal distributions were analysed using autoregressive integrated moving average (ARIMA) models.
Results
A total of 12.033 data, accounting for 7.491 men (mean age 47.46±13.51 years, range 18–91 years), were included. Mean testosterone serum levels (5.34±2.06 ng/dl, range 1.70–15.80 ng/dl) showed a seasonal distribution with higher levels in summer ($P=0.008$). A direct relationship between testosterone levels and maximum, minimum and mean temperatures (Rho:0.019, $P=0.041$; Rho:0.023, $P=0.011$; Rho:0.021, $P=0.024$, respectively) and daylight duration (Rho:0.021, $P=0.020$) was highlighted. LH (mean 4.64±2.54 IU/l, range 1.00–15.00 IU/l) presented two peaks of secretion in autumn and spring ($P=0.001$ and $P=0.001$, respectively), independently from environmental parameters. No seasonal distribution was observed considering FSH serum levels (mean 5.51±3.24 IU/l).
Conclusions
A clear seasonal fluctuation of both LH and testosterone was demonstrated in a large cohort of adult men, although a circannual seasonality of hypothalamic-pituitary-gonadal hormones in humans could be not strictly evolutionarily required. Testosterone seasonality seems independent from LH fluctuations, which could be regulated by cyclic central genes expression, and more sensible to environmental temperatures and daylight duration.

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AEP807

Genetic background and previous androgenization are associated with reproductive and non-reproductive outcomes of Gonadotropin-mediated pubertal induction in Congenital Hypogonadotropic Hypogonadism (CHH)

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CHH is a rare disease with a relevant genetic background, and is characterized by a failure to enter (complete forms) or to complete (partial forms) pubertal development. It requires a treatment to allow the completion of puberty, and in male this goal can be achieved either using testosterone replacement therapy or administering gonadotropins (Gn); the latter allows both testicular development and the endogenous testosterone production. There are few studies evaluating the therapy with Gn in CHH pubertal induction and there is no consensus on the protocol to be used. In this retrospective analysis we aimed to (i) investigate clinical and biochemical predictors of testicular response to Gn-induced puberty in CHH; (ii) study the non-reproductive outcomes of this treatment (height, body proportions) and their determinants. We retrospectively studied 19 CHH male patients, undergoing two years of Gn-mediated puberty induction with FSH and hCG, started between the ages of 14 and 23 years. For each patient clinical history, physical examination, hormonal evaluation, and genetic analysis using Targeted Next Generation Sequencing for CHH genes were performed; 8 patients performed a semen analysis (SA) at the end of their treatment. The Mann-Whitney test and multiple regression analysis showed a lesser increase in testicular volume after 24 months of induction, to be significantly associated with: (i) cryptorchidism; (ii) a positive genetic background; (iii) a complete form of CHH. We found no significant correlation with the cumulative dose of hCG administered in 24 months. We found no association with the results of SA, probably due to the low numerosity. The multiple regression analyses investigating the eunuchoid habitus and a measure of the difference of subject's final height from his target (deltaSDSth), found a significant relation with: (i) the age at the beginning of the induction; (ii) the duration of growth during the induction; (iii) for deltaSDSth, also the bone age before the induction. The duration of growth during induction resulted to be associated with previous testosterone priming and with partial forms of CHH. In conclusion, this study shows that genetic forms of CHH, as well as cryptorchidism, are negative predictors of testicular response. This could be because they determine a complete GnRH deficiency since intrauterine life. We also found that the eunuchoid habitus and deltaSDSth are associated not only with a delay in the treatment, but also with the duration of growth during the induction, which is apparently related to previous androgenization.

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AEP808

Androgen receptor inhibition by 4, 4' DDE is reduced by mutations in the BF3 site

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Androgen receptor (AR) is an important target for inhibition by some endocrine disrupting chemicals. Some diphenyl compounds inhibit AR activity by binding to a hydrophobic surface binding site, BF3. A similar diphenyl structure is found in 4.4' DDT and its breakdown product 4.4' DDE. Previous results showed that DDT, DDE, and related compounds induced the release of bound dihydrotestosterone from the AR ligand binding domain with IC_{50} values ranging from 54 to 82 uM. We tested whetherDDE may act as an EDC by binding to BF3 and inducing allosteric changes in the AR structure. Five mutant AR genes with single amino acid changes in the BF3 site were tested for differences in the ability of DDE to disrupt AR activity. The five mutations tested were F673K, F673W, G724R, G724M, and L830D. An AR reporter system was introduced into HEK293 cells by transient transfection and AR activity was measured using a dual luciferase assay. The response of the AR protein was measured with varying concentrations of dihydrotestosterone in the presence and absence of DDE. DDE inhibited the activation of AR by dihydrotestosterone under these conditions. The inhibition of AR activity by DDE was reduced by the mutations in the BF3 site. These results suggest that DDE acts as an endocrine disrupting chemical (EDC) by interacting with the BF3 site and allosterically regulating AR activity.

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AEP809

Computational study of the allosteric effects of the androgen receptor BF3 site mutations on steroid unbinding

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Experimental results have shown that the presence of endocrine disrupting chemicals (EDCs) such as the diphenyl compound DDT and its analogue DDE, allosterically cause the release of the stably bound dihydrotestosterone (DHT) from the steroid binding site of the Androgen Receptor (AR) ligand binding domain. It was hypothesized that EDCs mediate this effect via binding to the Binding Function 3 (BF3) surface binding site. Mutations of three BF 3 amino acids (F673K, F673W, G724R, G724M, and L830D) showed that the ability of DDE to inhibit AR activity was reduced, suggesting that DDE binds to the BF 3 site and allosterically regulates AR activity. In this study, the Induced Fit Docking protocol of the Schrodinger software was used to dock DDE into the BF 3 site of the wild type AR ligand binding domain as well as the five mutant BF 3 sites. The docking poses generated

for each receptor were clustered and representative structures were selected. The energy of interaction between DDE and the BF 3 site amino acids was evaluated for each of the selected docks of the wild type and mutant receptors. The relationship between the energies of interaction and the experimental results for DDE inhibition of the mutant AR activities is discussed. Additionally, stochastic dynamics were run on the wild type and mutant AR receptors using the Schrodinger software and the output was analyzed using the program Caver for the identification of potential exit channels for the bound steroid ligand. This analysis assesses the stability of the wild type and mutant AR receptors and indicates ways that the steroid may be able to unbind from the receptor in the presence of DDE in the BF3 site and how the mutations in the BF3 site affect that process.

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AEP810

Prenatal programming of hepatic lipid metabolism: Sex, hormones and lifelong health

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Background
The potential for a healthy life is programmed by *in utero* development. Fetal development is impacted by perturbed hormonal signalling, with lifelong consequences. Polycystic Ovary Syndrome (PCOS), affecting over 10% of women, is an important condition linked to an altered prenatal endocrine environment. Women with PCOS have increased androgen concentrations, including during pregnancy. Increased prenatal androgen exposure is associated with a PCOS-phenotype in adult life, including insulin resistance, fatty liver and obesity. Male offspring of women with PCOS develop dyslipidaemia and hyperinsulinemia. We used an ovine model of prenatal androgen exposure, faithfully recreating PCOS offspring phenotypes, to provide crucial mechanistic understanding of metabolic disturbances programmed *in utero* manifesting in adolesence.
Methods
Ovine fetuses were directly injected with 200 µl of testosterone propionate (PA; 20 mg) or vehicle control (C) at day 62 and 82 of gestation. Male offspring (C, $n=14$; PA, $n=14$) and female offspring (C, $n=10$; PA, $n=15$) were studied during adolescence. Hepatic transcriptome and proteome were determined (Illumina RNA sequencing and LC-MS/MS respectively). Plasma proteins and analytes were measured using LC-MS/MS, ELISA and clinical biochemistry autoanalysers. Statistical analysis between C and PA groups was carried out using pairwise comparisons, with false discovery rate correction, accepting adjusted $P<0.05$ as significant.
Results
Prenatally androgenised males and females displayed multiple metabolic perturbations, including hyperinsulinemia, dyslipidaemia, fatty liver, increased fibrosis, cholestasis-like phenotype. These were not all present in both sexes, with striking sex specificity in terms of lipid handling and liver function. PA females had increased plasma free fatty acids (FA), normal plasma triglycerides (TGs) concentrations, but increased hepatic TGs accumulation. This was coupled with reduced hepatic beta and omega oxidation potential. PA males had increased plasma FA, TGs and cholesterol concentrations in the absence of increased hepatic TGs accumulation. PA males displayed increased hepatic mitochondrial uptake of FA, however, they had decreased expression of genes and proteins involved in mitochondrial oxidative phosphorylation. This mismatch between mitochondrial FA oxidation without concomitant up-regulation of mitochondrial respiratory chain activity resulted in increased hepatic content of reactive oxygen species.
Conclusion
In both sexes, but with different mechanisms in terms of altered hepatic function, lipid handling in the liver was perturbed in postnatal life, as a legacy of prenatal androgen excess. Not all of these health-relevant outcomes were found in each sex however, demonstrating that sex-specificity must be accounted for in understanding of how the prenatal environment colours lifelong health.

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AEP811

Urinary bisphenol A (BPA) and its relation to insulin growth factor (IGF) system in polycystic ovary syndrome

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Objectives
There is a growing evidence suggesting an impact of endocrine distrupting chemicals, including bisphenol A (BPA) on human reproduction. Insulin growth factors (IGF) play signifcant role inhuman reproduction. However the relationship between BPA and IGF system is unknown. Aim of the pilot study was to assessthe relationship between urinary BPA (U-BPA) and insulin growth factors (IGF-1, IGF-2, IGFBP 3) as well as metabolic parametersin PCOS women.
Subjects and methods
The study included 76 Caucasian womenof mean age 28.8 ± 5.7 yearsdiagnosed with PCOS. Fasting blood samples were analyzed for biochemical parameters, IGF-1, IGF-2 and IGFBP3. U-BPA was measured in the morning urine sample using high pressure liquid chromatography (HPLC). BPA level of 2.14 mg/g creatinine were usedas the cut-off for high or low levels of this xenoestrogen and served for selection of patients into two groups.
Results
PCOS women with high U-BPA had significantly higher serum insulin ($P=0.0291$) and HOMA IR ($P=0.0371$) as compared to those with low U-BPA. Both groups did not differ in parameters of lipid metabolism. There were no significant differences in the serum IGF-1 ($P=0.36$) and serum IGF-2 ($P=0.3$) between both groups. Women withlow U-BPAdemonstrated higher serum IGFBP3 ($P=0.04$). In all group of PCOS women U-BPA negatively correlated with IGF-2 ($r=-0.25$, $P=0.04$) and IGFBP3 ($r=-0.54$, $P=0.0032$).IGF-1 tended to be lowerin women with high BPA, however correlation with U-BPA was borderline ($r=-0.2$, $P=0.068$).
Conclusion
U-BPA is in negative relationship with IGF-2, IGFBP-3 and borderline with IGF-1 in PCOS women. This indicates a possible suppressive effect of BPA on ovarian function in polycystic ovary syndrome through suppression of IGF system.

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AEP812

Congenital adrenal hyperplasia due to 3-beta-hydroxysteroid dehydrogenase deficiency

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Congenital adrenal hyperplasia due to 3-beta-hydroxysteroid dehydrogenase deficiency.
Introduction
Congenital adrenal hyperplasia is a heterogenic group of disorders. Shared feature is a deficiency of one of the enzymes which are necessary for steroid synthesis. Due to wide clinical spectrum and rarity of the disease diagnosis can be challenging. Hereby we present the case of the patient, who after prolonged period of time was finally diagnosed with 3-beta-hydroxysteroid dehydrogenase deficiency.
Case report
23-year old patient was admitted to endocrinology clinic due to hypogonadal hypogonadism. Pubic and axillary hair developed after unknown treatment commenced by urologist at the age of 11. Due to the lack of other signs and symptoms of puberty 17-year old patient was referred to endocrinology outpatient clinic. The diagnosis was not established. Patient did not continue diagnostic process. At the age of 23, he underwent appendectomy. Surgeon noticed typical features characteristic for hypogonadism and ordered endocrinologist consultation. Hypogonadal hypogonadism was diagnosed. Semen analysis results were within the norm. On physical examination performed during admission to hospital female-type fat distribution and pubic hair pattern was noticed. On ultrasonography size of testes was normal. CT of the adrenal glands revealed thickening of medial crus of left adrenal gland. Both LH, FSH and testosterone were decreased. On simulation test with GnRH, LH raised 12-times, while FSH 2-times. DHEAs and androstenedione were markedly elevated. Bone densitometry revealed osteoporosis. Urine steroid profile analysis was performed. It showed elevated levels

of: delta 5 steroids, especially pregnentriol. On the basis of laboratory and clinical findings 3-beta-hydroxysteroid dehydrogenase deficiency was diagnosed. Treatment with dexamethasone 1 mg daily and testosterone 1 injection per 3 weeks im was commenced. We noticed normalization of hormonal profile. Patient developed male secondary sex characteristics.
Conclusions
Diagnosis of non-classic form of congenital adrenal hyperplasia is challenging. In presented case proper treatment was vital to induce puberty, improve sexual function and quality of life.

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AEP813

Endocrinological aspects of woodhouse-sakati syndrome: Report of a new nucleotide variant DCAF17 homozygous mutation in the first family case in russia

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Introduction
Woodhouse-Sakati syndrome (WSS) is a rare autosomal recessive disorder characterized by diabetes, hypogonadism, hypothyroidism, sensorineural hearing loss, alopecia totalis, extrapyramidal findings and specific changes on ECG. This syndrome belongs to a heterogeneous group of neurodegenerative disorders and is caused by mutations of the DCAF17 gene. Treatment is symptomatic and patients are managed by multidisciplinary teams. About 90 cases were reported since 2008 when WSS was discovered.
Case report
We describe two sisters 18- and 29 years old affected by combined endocrine disorders such as diabetes, hypergonadotropic hypogonadism (with ultrasonic signs of uterine hypoplasia), hypothyroidism with negative thyroid auto antibodies, obesity and extrapyramidal symptoms such as dyslexia, sensorineural hearing loss, mild intellectual disability and dysmorphic facial features as well as alopecia totalis. GH, prolactin and ACTH levels were normal, but it should be noted that the younger sister had a low level of IGF. On ECG both of them had specific changes in the form of T-wave flattening. Brain MRI showed multiple brain cysts. Sisters differed in severity of clinical symptoms. The severity of the diabetic state is also varied between sisters. The younger sister had intact secretion of both basal and stimulated C-peptide levels, thus, she was prescribed sulfonylurea drugs with great glucose-lowering response. The older sister had a satisfactory basal and insufficient stimulated C-peptide levels, so she was switching to basis-bolus insulin therapy in conjunction with SGLT-2 inhibitors. They did not take levothyroxine and hormone replacement therapy with estrogen before. Common genetic, metabolic and mitochondrial disorders were excluded. WSS was suspected. Sequencing of DCAF17 gene detected new nucleotide variant NM_025000.3: c.1422+3G>T in homozygous state. This nucleotide variant has not been previously described.
Discussion
In the case of combinations of several endocrine pathologies with different characteristic features, genetic testing plays an important role. Thus, we can assume the progression of the disease as well as provide an integrated personalized approach to treatment. WSS was previously described in Arabian families and this is the first case in Russian family. Since we expect that diagnostic methodology and our understanding of disease pathology, including genes, allelic variants will improve in the future, DNA banking of affected individuals should be considered.

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AEP814

Early impact of cross-sex steroids on body composition and metabolic profile in young transgender subjects

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Background
In females transitioning to males (FtM) and in males transitioning to females (MtF), exogenous cross-sex steroids are prescribed to favour development of secondary characteristics of desired sex, while endogenous hormone production is inhibited.
Aims and design
To study early impact of cross-sex steroids on body composition, metabolic profile and pro-inflammatory parameters in young transgender persons before and after 12 months of gender-affirming hormonal treatment. Data of non-obese FtM subjects ($n=45$; 22.8±4.4 years) and MtF subjects ($n=28$; 24.8±5.9 years), followed in the University Hospital of Nancy were retrospectively analysed.
Results
In FtM subjects, testosterone administration led to a significant increase in haemoglobin (13.9±1.6 g/dl vs 15.5±0.9; $P<0.01$), and uric acid (41.2±6.2 mg/l vs 53.1±8.7; $P<0.01$), associated with a significant decrease in PRL (16.9±4.5 ng/ml vs 9.6±3.2; $P<0.05$). Pro-inflammatory indices tended to increase: AST/lymphocyte ratio (8.3±2.6 vs 9.8±3.4; $P=0.08$). An android fat distribution was enhanced with an increase in visceral adipose tissue (VAT) (260±217 g vs 368±280; $P<0.01$). There was a strong relationship between VAT and the following parameters: BMI, android fat mass, trunk/limb fat mass ratio, android/gynoid fat mass ratio; and between increase in VAT and in haemoglobin levels. In MtF subjects, a significant decrease in haemoglobin (15.4±1 g/dl vs 14.4±0.8; $P<0.05$) and in TSH (2.1±1.2 mIU/l vs 1.1±0.6; $P<0.05$) level was observed, without meaningful effects on body composition or metabolic profile.
Conclusion
Marked changes in body composition and in metabolic parameters are present in transgender subjects already after the first year of the cross-sex hormonal treatment. Significant increase in in VAT in lean transgender men may confer an increased cardio-metabolic risk in this subpopulation. Early assessment appears necessary to identify the subjects at risk and to individualise treatment regimens. Prospective long-term studies including a large sample size are needed to evaluate effects of early hormonal changes on the risk for cardiovascular diseases in MtF and FtM subjects.

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AEP815

The frequency nonclassic congenital adrenal hyperplasia in adolescent girls with primary oligomenorrhea and amenorrhea

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Objective
Nonclassic congenital adrenal hyperplasia (NCCAH, NCAH) or late onset congenital adrenal hyperplasia (LOCAH) is a specific type of congenital adrenal hyperplasia due to P450c21 (21-hydroxylase) deficiency with variable degrees of postnatal androgen excess, is sometimes asymptomatic (Kohn B *et al.* 2010; Speiser PW *et al.*, 2010). To study the frequency NCCAH in adolescent girls.
Patients and methods
The prevention examination of 2527 adolescents- schoolgirls (aged 12–17 yrs, mean age was 15.5±1.9 years) was carried. The main outcome measures were primary oligomenorrhea and amenorrhea. Adolescent girls without menstrual disorders formed the control group ($n=50$). A full clinical examination, hormonal analysis and pelvic ultrasound examination were conducted. CYP21A2 genotyping in girls with elevated 17-OH progesterone hormone levels (basal 17-OHP concentration ≥2 ng/ml (6 nmol/l) was performed. This study was carried out in accordance with the Helsinki Declaration. Data was analyzed using SPSS Statistics v 24.0.0.0. Data was compared using chi-square test and $P\leq0.05$ was regarded as statistically significant.
Results
Primary oligomenorrhea was present in 22%, primary amenorrhea – in 3 girls. The investigation showed that in 7 girls with oligomenorrhea was diagnosed nonclassic congenital adrenal hyperplasia due to P450c21 (21-hydroxylase deficiency). In all cases the first symptom was premature pubarche. All these girls have demonstrated hyperandrogenemia, high 17-OH progesterone hormone levels, advanced bone age, mammary hypoplasia, multifollicular ovaries. In the control group hyperandrogenemia was diagnosed in 1% and multifollicular ovaries – in 8% girls, mammary hypoplasia in 1 girls ($P<0.01$).
Conclusions
In our study nonclassic congenital adrenal hyperplasia was found in 7 (0.3%) adolescent girls. The phenotypic presentation of NCCAH in the

adolescentgirls included symptoms of hyperandrogenia such as premature pubarche, hirsutism, primary oligomenorrhea, advanced bone age, mammary hypoplasia, multifollicular ovaries.

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AEP816

Relapsing meningiomas in a transfemale treated with cyproterone acetate. Case and literature review

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A 40-year-old transfemale, regularly treated with oral estradiol (2 mg per day) and CPA (100 mg per day) for the last 15 years, presented with two asymptomatic intracranial lesions on compatible with meningiomas. Gender dysphoria since the age of 14, begins treatment in 2006. Paranoid schizophrenia at age 17. She referred to occasional headaches, without neurological defect. In the year 2013, a magnetic resonance imaging (MRI) scan revealed an expansive lesion over the sphenoidal planum. Prior MRI in 2007 was normal. Complete endoscopic resection was performed via intranasal of the meningioma of the sphenoidal planun. The immunohistochemical and morphological tests revealed a WHO grade I meningioma. Annual follow-up using contrast-enhanced MRI scan was performed after that. In 2018, the MRI scan showed the presence of one menigioma of 1.1 cm in the right frontal area and another of less than 1 cm at the level of the anterior clinoid processes. CPA was discontinued and was substituted with triptorelin acetate Our patient was treated for more than 10 years with cyproterone acetate with the appearance of a new menigioma again. The patient maintained high doses of CPA due to lack of alternative and severe hirsutism. It showed a recurrence of multiple of meningiomas during the follow-up. Our case confirms the clinical association between the administration of CPA and the presence of menigioma. These menigiomas appear after 5 years of treatment with high dose CPA. Proper treatment of the initial tumor does not exclude withdrawal of the CPA because of recurrence and multiple meningiomas in other brain locations. The occurrence of meningiomas in transfemale is uncommon and asymptomatic multiple tumors should be considered with the use of CPA. CPA should be removed. A literature review were done

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AEP817

Hutchinson – gilford progeria syndrome – a portuguese rare case

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Introduction
Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare disease (1:4 million) characterized by a fatal premature aging. There are 162 cases worldwide, five of them in Portugal. It is caused by a sporadic autosomal dominant mutation in LMNA gene that encodes an abnormal variant of the laminin-A protein, named *progerin*. Although most babies born looking healthy, they begin to display some characteristics of Progeria around 18–24 months of life. The earliest signs are tightness of the skin, growth failure and loss of body fat and hair. Other signs include orthopaedic, ophthalmologic and cardiovascular disease. Without Progeria-specific treatment, children die of atherosclerosis (heart disease or stroke) at an average age of 14.5 years. The intellect of children is unaffected. Pathophysiology maintains unclear. The 'Progeria Research Foundation' funds research to find new treatmentsfor Progeria. There is currently no cure for Progeria.
Case report
21-years female with HGPS caused by an 1824 C>T mutation in the exon 11 of LMNA gene. No family history of HGPS. First signs of disease at 4.5 months. Personal history of multiple fractures and dislocation of inferior members, hypermetropy, arterial hypertension, cardiac valvular disease, left ventricular hypertrophy, hypertriglyceridemia, hyperuricemia, palmar warts, subclinical hypothyroidism, multinodular goiter and secondary amenorrhea since 18 years. She is regularly monitored by orthopaedist, ophthalmologist, cardiologist, dermatologist, endocrinologist and gynaecologist. She maintains regularly follow-up at the Boston Children's Hospital and takes part of a clinical trial with Lonafarnib – a farnesyltransferase inhibitor. She is followed up in an Endocrinology-Transition consultation since the age of 18, after initial follow-up at the Pediatric Hospital, for unmedicated subclinical hypothyroidism and multinodular goiter with infracentimetric cystic nodules. At the last evaluation, patient maintains subclinical hypothyroidism (negative autoimmunity) with no need of medication, medicated hypertriglyceridemia and prediabetes. Cranioencephalic MRI was normal.
Discussion and conclusion
The clinical case intends to demonstrate the rarity of this syndrome that is associated with multiple pathologies/comorbidities, needing regular monitorization throughout the life, by a multidisciplinary team, including medical and surgical teams. Due to the rarity of the disease, research and development of effective therapies becomes more difficult. The main of drugs currently available is reducing complications of the syndrome. Supportive therapy is also extremely relevant as it improves patients' quality of life. Patient associations and international exchanges have been shown to be fundamental for families. https://www.progeriaresearch.org/

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AEP818

Epidemiology, clinical features and management of multiple endocrine neoplasia Type 1 – a two-center study

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Background
Multiple Endocrine Neoplasia Type 1 (MEN1) is a rare, autosomal dominant disease characterized by the coexistence of at least two of the following: primary hyperparathyroidism (PHPT), neuroendocrine tumors (NET) and pituitary tumors. The aim of the study was to evaluate epidemiology, clinical features and management of MEN1 patients in two referral centers in Warsaw, Poland.
Material and methods
Study group consisted of 52 patients, aged from 18 to 74 (mean: 45.5, S.D. = 14), diagnosed with MEN1 and followed-up from 2015 to 2020 in two tertiary centers. 71% of patients were women, 29% were men. Data was collected using a pre-prepared form concerning demographics, medical and family history, quality of life, as well as, physical examination, laboratory, imaging, histopathological and genetic tests results.
Results
In the studied group, the first symptoms of the disease appeared on mean age of 29.6 (range: 9–60; S.D. = 12.0). The most often were: nephrolithiasis (33%), hypercalcemia (13%) and menstrual disorders (11% of women). The diagnosis of MEN1 was made on average age of 36.9 (S.D. = 13.1). Only 37% underwent genetic testing. In 52% patients the first diagnosed component of disease was PHPT, in 33% pituitary tumor, in 13% NET. 94% of subjects developed PHPT, 85% NET, 67% pituitary tumor. Every second patient manifested all three main components of the disease. Based on dual-energy X-ray absorptiometry, 76% of patients had reduced bone density and 8% of them underwent a pathological fracture. Nephrolithiasis was found in 60% of people and peptic ulcer disease in 26%. In addition to typical for MEN1, 15% of patients developed other malignancies: papillary thyroid, clear cell kidney, breast, endometrial cancers and melanoma. 85% was also diagnosed with benign neoplasms of: adrenal glands (45%), kidney/liver/spleen cysts (31%), lung nodules (13%). Up to 62% of people underwent at least one parathyroidectomy, yet 55% of them still have hypercalcemia. In the group of patients suffering from pituitary tumors 31% underwent surgery, whereas in the case of NET – 55%. Treatment with somatostatin analogues was initiated in 49%.
Conclusions
In this group, MEN1 was diagnosed with a long delay from the disease onset. The discrepancy between number of women and men being followed-up may indicate its underdiagnosis in men. PHPT was proved to be the most difficult component to manage. Frequent coexistence of other tumors, both malignant and benign, has also been demonstrated. These results suggest a need for improvement at every level of healthcare, from detection to management.

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AEP819

Fetal anogenital distance is longer in polycystic ovary syndrome mothers

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Aim
Anogenital distance (AGD) is a biomarker for the prenatal hormonal environment. Scarce evidence exists regarding the effect of prenatal androgen exposure in mothers with polycystic ovary syndrome (PCOS) on the human fetal AGD. The aim of the study was to assess the prenatal sonographic measurement of AGD in fetuses of PCO mothers vs the general population.
Materials and methods
AGD was measured prospectively infetuses at 26–37 weeks of gestation, using 2D ultrasound, in an axial view, at the level of the fetal perineum. Data was compared to fetal AGD nomograms, and the Z score was evaluated. Maternal and fetal characteristics were analyzed.
Results
27 PCOS mothers carrying singleton fetuses were recruited (12 females, 15 males). Mean gestational age at measurement was 31.2 weeks±3 days. Mean AGD, adjusted for gestational age and gender, was significantly higher in the PCOS (21.13 mm±5.9 mm) compared to the control (17.19 mm±5.45 mm) group, respectively, $P<0.001$. Mean AGD-PCOS centile was 86.04 (±18.22). Z score was not statistically different in the males (2.035±2.1950) compared to the females (2.185±1.3834). The AGD measured in fetuses of mothers with diabetes (52% of the study group) was significantly longer compared to the general population (19.74 mm±4.8 mm vs 15.11 mm±4.77 mm $P<0.001$).
Conclusions
This is the first report demonstrating a longer AGD in fetuses of mothers with PCOS. AGD may play a role as a biomarker of the intra-uterine androgen milieu, specifically in PCOS. Importantly, this might change the way we approach and treat PCOS pregnancies.

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AEP820

BMI may be a better predictor of cardiovascular risk than PCOS phenotype in a population of reproductive age PCOS patients

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Introduction
Women with polycystic ovary syndrome (PCOS) are considered to have increased risk of cardiovascular disease (CVD), even though the syndrome encompasses hugely varying phenotypes. Research into CVD prevention demonstrated a variety of biochemical and ultrasound (US) markers predicting risk in the general population, but those are sparsely utilised for PCOS, in part due to the patients' therapeutic goals.
Aim
To evaluate if PCOS type or BMI are better predictors of cardiovascular risk, by comparing them to biochemical and US markers.
Material and methods
We recruited 138 women with PCOS in the reproductive age from the Endocrinology Unit in 2009. We subdivided them by Rotterdam criteria into 4 types (A, $n=74$; B, $n=22$; C, $n=11$; D, $n=31$), and by BMI into normal weight (18.5–24.9 kg/m^2, $n=45$), overweight (25–29.9 kg/m^2, $n=42$) and obese (>30 kg/m^2, $n=51$). Biochemical analyses measured: OGTT and fasting glycemia, fasting insulin, total cholesterol, LDL, HDL, triglycerides. Derived parameters: HOMA2 insulin resistance index, free testosterone index (Vermeulen formula, fTv). Carotid intima media thickness (cIMT), endocardial fat thickness (EFT) and brachial flow mediated dilation (FMD) were measured using B-mode US.
Results
We did not find any difference in the analysed variables among the four PCOS phenotypes. Conversely, by dividing patients in BMI categories we found increasingly higher values of systolic blood pressure ($P=2\times10^{-11}$), cIMT ($P=2\times10^{-8}$), EFT ($P=3.7\times10^{-10}$), triglycerides ($P=10^{-4}$), HOMA2 ($P=10^{-12}$) and fTv ($P=0.001$), and lower values of HDL ($P=3\times10^{-6}$) and FMD ($P=0.004$), going from normal to obese BMI categories. There was no statistical difference in the prevalence of different PCOS phenotypes based on BMI subgrouping ($P=0.633$), whereas there was a higher prevalence of diabetes in the obese BMI group with respect to overweight or normal weight groups (31.4 vs 9.8 vs 2.3%, $P=0.0002$).
Conclusion
In our group of PCOS women in the reproductive age, BMI was shown to be a better predictor of cardiovascular risk compared to PCOS phenotype categorisation.

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AEP821

Prevalence and prognostic factors of dysglycemia in women with polycystic ovary syndrome: Findings from large caucasian cohort

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Background
Insulin secretory defects and insulin resistance exists in women with polycystic ovary syndrome (PCOS) and are prerequisites for the development of type 2 diabetes (T2D). we aimed to determine the prevalence of T2D, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), as well as the factors associated with these dysglycemic conditions in this population.
Methods
1614 PCOS women of Caucasian origin (Rotterdam criteria) with a mean age 25.14±5.56 years and BMI 27.34±7.09 kg/m^2 comprised study group, whereas 359 normally ovulating, not hyperandrogenic women of comparable age and BMI, served as controls. This was an observational study and evaluation of biochemical/hormonal profile, ovarian ultrasound and as well oral glucose tolerance test was carried out in all studied subjects. Diabetes/intermediate hypeglycemia was categorized according to WHO criteria and PCOS subgroups was based on the Rotterdam criteria.
Results
In the PCOS group 2.2%, 9.5% and 12.4% of subjects had T2D, IGT and IFG, respectively. In control group 1.11%, 7.5% and 8.9% had T2D, IGT and IFG, respectively. When existence of T2D was stratified according to age and BMI, no difference was found among age and BMI subgroups or PCOS subgroups. In patients aged 17–22 years, T2D was detected in 3 lean and 2 obese subjects. The corresponding distribution for patients aged 22–30 years was 4 lean, one overweight and 2 obese, whereas in those older than 31 years, 2 overweight and 5 obese suffered from T2D. Free Androgen Index, waist to hip ratio and LDL levels were significantly higher in T2D compared to PCOS women with normal glucose metabolism. Diagnosis of T2D was significantly associated with Free Androgen Index (r: 0.469, $P<0.05$), while subjects with either IFG and IGT had positive association with BMI, WHR, FAI and HOMA-IR. In controls, T2D, IGT and IFG were positively associated with BMI and androgen concentrations. Conclusions: The prevalence of T2D and IGT is significantly higher in our large cohort of PCOS women compared to controls. Existence of T2D is irrespective of age and BMI, and seems to be inherent for PCOS women. Hence, evaluation of glycemic status in PCOS women using OGTT is supported.

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AEP822

An assessment of the level of physiological stress in terms of release of cortisol, epinephrine, norepinephrine, prolactin and growth hormone and their relationship with ghrelin in normal and short stature children

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The short children have lower social competence and show more social problems than children with normal stature. The physical appearance has consequences in terms of how short stature children are judged and treated by others as they can be teased or bullied due to short stature, which may affect future prospects of finding a job or a spouse. These psychosocial stressors are risk factors for the psychological adjustment for children of short stature. Stress responses are activated by hypothalamo-pituitary-adrenal (HPA) axis by releasing cortisol, a marker of stress. Another hormone, ghrelin, also stimulates stress related HPA axis resulting in the release of cortisol. Both cortisol and ghrelin concentrations increase in parallel after psychological stress. The present study was designed to identify the level of physiological stress in terms of release of cortisol, epinephrine (E), norepinephrine (NE), prolactin (PRL), growth hormone (GH) and their relationship with ghrelin in normal and short stature children. ELISA was used for analysis of plasma cortisol, prolactin, E and NE and RIA was used for analysis of plasma GH of 50 normal school attending children and 35 short stature girls and boys. Data were analyzed using Student's t test, ANOVA and Pearson correlation r. The concentrations of stress hormones such as cortisol, E and NE were higher in short stature children at puberty as compared to normal school attending children. The levels of GH and PRL were significantly decreased in short stature children than controls. In addition, the levels of plasma ghrelin were positively correlated with plasma cortisol, E, NE, GH and PRL levels in normal subjects while negatively correlated in short stature children. In conclusion, this study demonstrated higher concentrations of stress hormones, cortisol, E and NE in short stature children at puberty than normal school attending children indicating that short stature children were at a higher level of stress.

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AEP823

Testosterone levels are the main determinant of prostate volume in men with chronic spinal cord injury

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Men with spinal cord injury (SCI) exhibit a prostate volume significantly smaller compared to age-matched able-bodied men[1–3]. As men with chronic SCI (lasting more than 1 year) also display a very high prevalence of androgen deficiency[4,5], a protective role of low testosterone against prostate enlargement could be hypothesized in this population. This study aimed to identify independent determinants of prostate volume in men with chronic SCI. As assessed by trans-rectal ultrasonography, the median value of prostate volume in 138 men with chronic SCI (mean age: 53±18 years) was 23.43 ml. Men with prostate volume smaller than 23.4 ml exhibited significantly lower levels of total testosterone (TT) and calculated free testosterone (cFT), as well as a higher prevalence of biochemical androgen deficiency (TT lower than 264 ng/dl), that in the entire population was observed in 29.7% (41/138) of subjects. At the univariate analysis, a larger prostate volume was associated to higher TT ($P=0.00001$) and cFT ($P=0.001$), SCI level below T12 ($P=0.007$), more advanced age ($P=0.04$), lower body mass index ($P=0.04$), higher functional independence score ($P=0.06$), higher values of prostate-specific antigen ($P=0.12$) and shorter duration of the injury ($P=0.21$). However, at the multiple regression analyses, an independent and positive association only persisted between prostate volume with either TT or cFT levels, and, to a lesser extent, with age and a level of spinal lesion below T12. A prostate volume below the median value (23.4 ml) was observed in 91.4% (32/35) of patients with both biochemical androgen deficiency and spinal lesion level at or above T12, but in only 16.5% (2/12) of patients with both normal androgen levels and spinal lesion level below T12 ($P=0.001$). In conclusion, lower testosterone levels and, to a lesser extent, a younger age and a spinal lesion level at or above T12 represent the only variables exhibiting an independent association with a smaller prostate volume in men with SCI. It could be hypothesized that the combination of these factors could be protective against the development of proliferative prostatic diseases, including benign prostatic hyperplasia. Prospective studies might assess the validity of this hypothesis.

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AEP824

Transphobic attitude: In physicians who play an active role in the gender transition process

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Transphobia is expressed as negative attitudes, emotions and actions towards transgender individuals or transsexualism. The aim of this study is to investigate the existence of transphobic approaches towards transgender individuals in physicians in different clinics that play an active role in the gender transition process. It was planned to include physicians from the disciplines of psychiatry, endocrinology, gynecology, urology and plastic surgery. A questionnaire was sent to these physicians via internet and the participants were asked to answer ''the Genderism and Transphobia Scale'' and sociodemographic questions such as academic title, type of institution, age, gender, place of birth and residence, marital status, sexual orientation and religious belief. Also, no names and surnames were requested from these people. Increased scale scoreshows the presence of higher transphobia. The number of physicians who completed the study on the internet was 455. The mean age was 37.03±9.59 years. The male to female ratio was 1.12. Of the participants, 23 (27%) were psychiatrists, 107 (23.5%) were endocrinologists, 93 (20.4%) were gynecologists, 88 (19.3%) were urologists and 44 (9.7%) were plastic surgeon. 203 (44.6%) of the participants defined themselves as belong to a religion, 106 (23.3%) as deist, 91 (20%) as religious and 55 as atheist. And, 94.9% of the participants were heterosexual. According to disciplines, there was a significant difference between groups in term of the mean total scores of transphobia scale ($P<0.001$). In the post-hoc analysis to understand the reason for the difference, scale scores of psychiatrists were significantly lower than endocrinologists, plastic surgeons, and urologists, and did not differ from gynecologists. Morever, we found that urologists' scale scores were significantly higher than gynecologists. When the participants were categorized according to their religious self-definition; the mean total scores of scale were significantly different between groups ($P<0.001$). While the mean scores of those who define themselves as atheists and deists were lower than those who belong to a religion and religious, Psychiatrists are in an important role in the psychotherapy process, which is used to diagnose transgender individuals and to cope with the difficulties these individuals experience in society and in the gender transition process. For this reason, it can be thought that psychiatrists show less transphobic approaches than other disciplines. This study shows that transphobia may be at different levels according to the discipline of physicians and there may be differences as a result of individual characteristics.

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AEP825

Influence of air pollutants of vehicular origin in hormonal and seminal parameters of traffic controllers

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Sao Paulo is the most populous city in Brazil and its huge number of vehicles contributes for a higher concentration of air pollutants that may interfere in human fertility. The aim of this study was to evaluate the influence of air pollution of vehicular origin on hormonal and seminal parameters of traffic controllers. Clinical history, physical examination (testicular volume, presence of varicocele, cryptorchidism, malformations), hormonal (estradiol, LH, FSH and total testosterone) and seminal parameters (concentration, motility, morphology by WHO´s criteria and Kruger´s strict criteria, leukocytes detection test, CK, ROS and anti-sperm antibody tests) were carried out in 62 traffic controllers (exposed group) and in 210 proven fertile men from the pre-vasectomy group of Urologic Clinic at Hospital das Clinicas – University of Sao Paulo (control group). Exposition to air pollution was analyzed through the dispersion of pollutants recorded by Cetesb, generated in the software SURFER 8.0. Hormonal levels were at normal range in both groups: Estradiol ($P=0.119$), LH ($P=0.644$), FSH ($P=0.140$) and Total Testosterone ($P=0.365$). Traffic controllers presented bigger testicular volume than pre-vasectomy group ($P<0.001$). Sperm concentration was homogeneous in both groups ($P=0.395$): traffic controllers presented mean of 124.9×10^6/ml and pre-vasectomy group 110.1×10^6/ml. Exposed group presented total motility (60%) diminished than control group (65%) ($P=0.047$), as progressive motility was also diminished in the exposed group ($P<0.001$). The sperm morphologies as by WHO´s criteria (exposed group=12%; control group=20%), as by Kruger´s strict criteria (exposed group=3%; control group=6%) were significantly diminished in the exposed group ($P<0.001$). Sperm maturity marker CK was at normal range at both groups, but higher in the control one ($P<0.001$). Anti-sperm antibodies and ROS were elevated in both groups, however it was not significant ($P=0.382$ and $P=0.141$, respectively). Air pollution has a deleterious effect on sperm motility and morphology but not in male hormonal levels. It also causes elevation of ROS levels, indicating deficit in sperm function, and elevation of anti-sperm antibodies levels, suggesting that air pollutants would have transposed the blood-testis barrier. Testicular volume in the exposed group was higher than those measuredin the control group; we can suppose that it must occur due to an inflammatory reaction against the polluting agents. Although the significant difference in air pollutants concentrations between groups, no direct correlation to seminal parameters could be demonstrated.

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AEP826

Assessment of the status of the pituitary-gonadal axis in men who have been using androgenic anabolic steroids for a long time

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Background
The study of the state of the pituitary-gonadal axis (PGA) in users of anabolic androgenic steroids (AAS) is important. The severity of inhibition of luteinizing (LH), follicle-stimulating (FSH) hormones, total testosterone (Tt), inhibin B may depend on the type of AAS used, its doses, the simultaneous use of several types of AAS and the duration of their administration.
Aim
To evaluate the levels of LH, FSH, Tt and Inhibin B depending on the type, dose, pattern and duration of the use of AAS.
Methods
An observational prospective study was conducted among male AAS users. During the use of AAS, LH, FSH, and Tt levels were determined by the immunochemiluminescent method, and the inhibin B level was determined by an enzyme immunoassay. Data are presented as median and interquartile range. We used the Fisher's exact test, Spearman's Rank correlation coefficient. The differences were considered statistically significant at $P<0.05$.
Results
44 male volunteers were examined, median age 29 [27.75;34] years, the duration of the use of AAS were 6 [3.52; 7] months. AAS: testosterone propionate 97.7% ($n=43$), dihydrotestoserone derivatives 65.9% ($n=29$) and 19-nortestosterone 47.7% ($n=21$). One drug were used 18% ($n=8$), 2 drugs 50% ($n=22$), 3 drugs 32% ($n=14$) participants. Doses of injectable preparations varied: from 750 mg per week 25% ($n=11$), to 1000 mg 36% ($n=16$), above 1000 mg 39% ($n=17$) men. Laboratory tests while using AAS: LH-0.2 mIU/ml [0.04; 0.47], Tt-4.34 ng/ml [1.05; 8.81]. The discrepancy between low levels of LH(0.2 mIU/ml) and normal testosterone levels is explained by exogenous testosterone. In our study, men with high levels of Tt were 29.5% ($n=13$), and the maximum value of Tt was 45.56 ng/ml (157.96 nmol/l). In the study, the number of men with a LH level <1.24 mIU/ml were 84% ($n=37$) and Tt<3.4 ng/ml was 47.7% ($n=21$) participants. Inhibin B levels during AAS use: 131.7 [72.3;166.4] pg/ml. LH was lower when large doses of AAS were used ($P=0.003$), when more AAS was used together ($P<0.001$), and in cases of dihydrotestosterone ($P=0.018$) or 19-nortestosterone ($P<0.001$). Similar data were obtained for FSH, Tt, Inhibin B. A significant correlation was established between the duration of AAS use (–0.794; $P<0.001$), the amount of AAS (–0.411; $P=0.003$), the dose of AAS (–0.726; $P<0.001$), the type of AAS (–0.602; $P<0.001$) and LH levels.
Conclusion
A significant negative effect of the type, dose, duration of use and amount of simultaneously administered AAS on the levels of LH, FSH, Tt and Inhibin B were revealed.

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AEP827

Testosterone (T) is poorly related to sexual desire and Erectile Dysfunction (ED) in Young/Middle Aged Human immunodeficiency virus (HIV)-Infected Men

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Background
ED is highly prevalent in HIV-infected men. T leads sexual behavior in men, but preliminary data suggests that ED is poorly related to serum T in HIV-infected men.
Aim
To explore the relationship between sexual function and gonadal function in young/middle-aged HIV-infected men.
Methodology
Prospective, cross-sectional, observational study on HIV-infected men (age <50 years). Serum TT was assessed by the gold standard LC-MS/MS. Sex hormone-binding globulin (SHBG) was measured by chemiluminescent immunoassay and calculated free T (cFT) was obtained by Vermeulen equation. Biochemical hypogonadism was defined as TT levels below 320 ng/dl and/or cFT levels below 64 pg/ml. The validated International Index of Erectile Function (IIEF)-15 questionnaire was used to identify the presence of ED (score <25) and its degree. IIEF-5 was performed to check if it is reliable as IIEF-15 in this setting.
Statistical analysis
Continuous and categorical variables were compared using ANOVA univariate and Chi-Square test. Correlations were performed using linear regression models.

Results
315 consecutive HIV-infected men were enrolled (mean age 45.3±5.3 years; mean duration of HIV-infection 16.3±8.8 years). A total of 187 patients (59.7%) had ED at IIEF-15; 59 patients (31.5%) presented a severe form of ED (score <10). Considering gonadal function, 35 patients (11.1%) had T deficiency. Scores of EF ($P=0.039$) and sexual desire ($P=0.015$) domains were higher in hypogonadal than eugonadal men. Accordingly, the prevalence of ED raised to 71.4% among hypogonadal men. By considering ED severity, patients with severe ED showed a longer duration of infection ($P=0.039$) and lower cFT levels ($P=0.041$) than patients with mild ED. No difference was found for age ($P=0.224$) and TT levels ($P=0.110$). IIEF-15 score was inversely related to duration of infection ($R^2=0.030$, beta=–0.173, $P=0.002$) and patients' age ($R^2=0.020$, beta=–0.140, $P=0.013$).No significant correlation was found between IIEF-15 score and total T ($P=0.236$) and cFT ($P=0.126$). The erectile function domain at IIEF-15 directly correlated with IIEF-5 score ($R^2=0.545$, beta=0.778, $P<0.001$).
Conclusions
In our HIV-cohort of young/middle-aged men, the prevalence of ED and T deficiency were high being of 60% and 11%, respectively. Serum TT and cFT did not correlate with sexual function parameters, even though sexual desire was lower in men with hypogonadism. ED seems to be better predicted by other factors, such as the duration of infection in this clinical setting, rather than the gonadal status. Furthermore, IIEF-5 seems to be as reliable as IIEF-15 for ED diagnosis in HIV-infected men.

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AEP828

Partial androgen insensitivity: A case report

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Introduction
Androgenic insensitivity syndrome (AIS) is an X-linked genetic disease characterized by resistance to the actions of androgen in an individual with 46, XY karyotype. It is the most common cause of DSD in 46, XY individuals.
Case report
We report a case of a 16-year-old girl who consulted for primary amenorrhea and hirsutism. Our patient had a 9-year-old sister who was operated for an inguinal hernia and the anathomopathological study concluded to a testicular tissue. Physical examination revealed virilization signs: clitoridomegalia, deepening voice and muscle enlargement, female external genitalia and a blind ending vagina. Hormonal evaluation revealed markedly elevated testosterone (6.4 ng/ml), FSH, and LH serum levels. AMH level and dihydrotestosteronemia were low. HCG test showed an increasing testosterone level after HCG stimulation. Diagnostic imaging, including an abdominal ultrasound and a pelvic MRI, showed missing uterus and fallopian tubes and confirmed the presence of two solid structures compatible with gonads measuring 14 mm at the right and 24 mm at the left. Chromosomal analysis confirmed 46, XY karyotype with intact SRY. The patient underwent genetic testing, revealing no androgen receptor mutation. Therapeutically, the patient has benefited from a psychological support and bilateral gonadectomy is programmed especially since alpha foeto protein level was high.
Conclusion and comments
The androgen insensitivity is a rare pathology. Molecular diagnosis is achieved in almost all patients with complete AIS and in a lower frequency in PAIS individuals. In PAIS there is a risk of degenerancy in 20% of the patients, and bilateral gonadectomy is recommended in all individuals raised in the female social sex. In AIS, gender identity usually follows the sex of rearing, but sexual functioning and quality of life can be compromised, that's why it is important to keep patients in psychological care.

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AEP829

Gut microbiota and oral contraceptive use in polycystic ovary syndrome

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Context
Polycystic ovary syndrome (PCOS) is a common and complex endocrine disorder. Emerging animal and human data point out to various changes in microbiota that could be linked with the syndrome. However, the effects of therapeutic approaches on gut microbial composition in women with PCOS remain unknown.
Objective
We aimed to assess whether gut microbial composition is altered in overweight/obese women with PCOS and to determine potential impact of oral contraceptive (OC) use on gut microbiota.
Materials and methods
The current study included 17 overweight/obese patients with PCOS and 15 age- and BMI-matched healthy control women. At baseline, clinical, hormonal and metabolic evaluations and gut microbial composition assessment by 16S rRNA gene amplicon sequencing were performed after a 3-day standardized diet. Patients received dienogest-ethinylestradiol (2 mg/0.03 mg) therapy along with general dietary advice for three months after which all measurements were repeated.
Results
Women with PCOS had higher total testosterone (T) and free androgen index (FAI) levels than healthy control women whereas whole body fat mass, fasting plasma glucose, insulin and lipids were similar between the groups. Alpha and beta diversity did not show a difference between PCOS and healthy controls at baseline and remained unaltered after 3 months of OC use in the PCOS group. Relative abundance of Ruminococcaceae family was higher in PCOS patients ($P=0.006$) and did not show an alteration after treatment.
Conclusion
Relative abundance of Ruminococcaceae family is increased in women with PCOS whereas short-term OC use does not alter compositional features of gut microbiota in the syndrome.

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AEP830

Anti-müllerian hormone (AMH) as the primary marker for ovarian reserve in transgender male, with or without pcos, under cronic testosterone treatment

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Background
AMH represents a marker of ovarian reserve and is used in monitoring the effects of gonadotoxic drugs. In PCOS is higher and is an indirect marker of hyperandrogenism. In transsexual man(TM), high prevalence of PCOS is described and AMH provide information about ovarian reserve after exposure to testosterone.
Objective
To assess the prevalence of PCOS in young TM previously to testosterone treatment, study the evolution of AMH levels and differentiate it response patterns according to the presence of PCOS.
Material and methods
Retrospective cohort of TMtreated with testosterone followed between 2010–2018. Levels of AMH, Testosterone, Androstenedione, LH, FSH and Estradiol at baseline and at 6 months after intramuscular testosterone were analyzed. The AMH response was evaluated based on the presence of ovariananalytic hyperandrogenism (AH) previous to treatment (testosterone ≥ 0.7 ng/ml or androstenedione ≥ 5 ng/ml) with or without clinical PCOS (Rotterdam Criteria).
Results
Of 162 HT included, the mean age was 21 years (range 13–39). Baseline AMH 3.5 ng/ml (Interquartile range (IR) 3), Testosterone 0.4 ng/ml (IR 0.1), androstenedione 3.23 ng/ml (IR 1.89), FSH 4.3 mUI/ml (IR 3), LH 5.1 mUI/ml (IR 5) and estradiol 63 pg/ml (IR 79). 8% ($n=13$) of the sample had PCOS (median age19 years (range 15–33)) and 19% ($n=31$) had AH (median age 21 years (range 15–34)), without differences. A correlation was

observed between baseline levels of AMH and Testosterone: 0.2 ($P=0.01$) in the general group, 0.479 ($P=0.006$) in AH group and 0.549 ($P=0.051$) in PCOS. Table 1 shows the baseline levels of hormones in different groups. Table 2 shows the changes in AMH throughout the follow-up in different groups.

Table 1

Baseline hormones (ng/ml) Median (IR)	PCOS		*P*-value (U Mann-Whitney)	AH		*P*-value (U Mann-Whitney)
	Yes ($n=13$)	No ($n=149$)		Yes ($n=31$)	No ($n=131$)	
AMH	4.5(5.4)	3.4 (2.9)	0.229	3.8(4.0)	3.4(2.9)	0.55
Testosterone	0.7(0.34)	0.3 (0.1)	<0.001	0.7(0.4)	0.3(0.1)	<0.001
Androstenedione	5.6(1.32)	3.5(1.56)	<0.001	5.3(1.95)	2.9(1.5)	<0.001

Table 2

	Baseline	6 months	*P*-value (Wilcoxon test)
General group ($n=118$)	3.5(3.20)	2.8(2.50)	<0.001
PCOS ($n=8$)	4.45(7.55)	4.2(3.42)	0.528
AH ($n=21$)	3.6(4.20)	3(3.05)	0.029

Conclusions
The% of PCOS is not higher in TM compared to cis-women. AMH can be a good subrogated marker of PCOS and AH. The ovarian follicular reserve measured by AMH is not significantly damaged by treatment with testosterone in the short or medium term. This response is no different in TM with PCOS or AH.

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AEP831

The association of serum miR-27a and miR-320 level with glucose metabolism and insulin sensitivity in young women with polycystic ovary syndrome

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Introduction
Polycystic ovary syndrome (PCOS) is associated with an increased risk of insulin resistance. The involvement of microRNAs, small, non-coding molecules, in regulation of metabolic processes has been investigated. The role of miR-27a and miR-320 in regulation of glucose metabolism is documented. The aim of the study was to assess the level of circulating miR-27a and miR-320 in PCOS patients and to investigate its relationship with glucose metabolism.
Materials and methods
The studied group comprised 100 PCOS patients diagnosed with the Rotterdam criteria (age 24.3±3.7 years, BMI 25.2±5.3 kg/m^2), divided into phenotypes (I–33 patients; II–24 patients; III–21 patients; IV–12 patients), and 88 healthy women as a control group (age 25.4±4.3 years, BMI 23.4±3.3 kg/m^2). Anthropometric measurements, transvaginal ultrasound, assessment of sex hormones concentrations and oral glucose tolerance test (OGTT) were performed. Serum miR-27a and miR-320 levels were assessed with real-time polymerase chain reaction.
Results
The studied groups were similar in terms of age and BMI. Patients with PCOS presented higher glucose concentrations at 30 and 60 minutes of OGTT ($P=0.042$; $P=0.023$), higher insulin concentrations at 30, 60 and 120 minutes of OGTT ($P=0.049$; $P<0.001$; $P=0.013$) and lower Matsuda index ($P=0.001$) vs controls. Level of miR-27a was higher ($P<0.001$) and miR-320 was lower ($P<0.001$) in PCOS vs controls. Level of miR-27a was higher in phenotype I than in phenotype III ($P=0.021$).

Fasting glucose concentration correlated with miR-27a ($R=0.32$, $P=0.001$) and miR-320 level ($R=–0.28$, $P=0.006$) only in PCOS. In phenotype I, miR-27a level correlated with glucose at 0 and 120 minutes of OGTT ($R=0.45$, $P=0.009$; $R=0.36$, $P=0.043$), fasting insulin concentration ($R=0.44$, $P=0.011$), and Matsuda index ($R=–0.40$, $P=0.021$). In phenotype II, miR-320 correlated with glucose at 0 and 60 minutes of OGTT ($R=–0.41$, $P=0.044$; $R=–0.47$, $P=0.020$). In phenotype III, miR-27a correlated with glucose concentration at 60 minutes of OGTT ($R=0.45$, $P=0.038$). In the subgroup of women with PCOS and impaired fasting glucose (IFG)/impaired glucose tolerance (IGT), we observed higher miR-27a and lower miR-320 level, comparing to PCOS patients with normal glucose tolerance ($P=0.003$; $P=0.030$). In patients with PCOS and IFG/IGT, miR-27a level correlated with fasting insulin concentration ($R=0.50$, $P=0.029$).
Conclusions
Serum levels of miR-27a and miR-320 are altered in PCOS patients and may be linked with impaired glucose metabolism. The association of miR-27a and miR-320 with insulin sensitivity seems to be more pronounced in phenotype I. Circulating miR-27a and miR-320 could serve as potential biomarkers of glucose metabolism disturbances in PCOS.

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AEP832

Male hypogonadism and sarcopenia

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Background and aim
Low testosterone levels are known to be associated with unfavorable body composition and testosterone replacement is known to be associated with increased muscle mass and muscle strength. The aim of this cross-sectionalstudy is to evaluate the grip strength, appendicular muscle mass and physical performance and bone mineral densities of hypogonad male patients.
Method
75 hypogonad and 45 healthy control subjects were included in this study. The etiology of hypogonadism, follow-up and replacement durations were asked. The right and left handgrip strength were measured by a hand dynomometer to assessmuscle strength. Decreased muscle strength was defined as <27 kg in men. Appendicular skeletal muscle mass was detected with bioelectrical impedance analysis and gait speed was detected with 4 meter usual walking speed test to assess physical performance if the patient was sarcopenic. Bone mineral densities of the patient group were evaluated. Serum testosterone levels measured at 10th day of testosterone propionate injection were recorded.
Results
69 of the 75 hypogonad patients were hypogonadotrophic hypogonadism and 23 patients had panhypopituitarism. 66 of the patients were under replacement therapy but 42 of these patients had low serum testosterone levels according to reference range. The grip strength of the patient group was significantly lower than control group. 15 of the patients had muscle weakness. Appendicular skeletal muscle mass of these patients were normal. When all of the subjects were included, grip strength of the low testosterone group were lower and the BMI and Hba1c levels weresignificatly high. The total testosterone levels had a significant negative correlation with hand grip strength ($r=0.007$) but no correlation with BMD levels. When the patient group was evaluated according to testosterone reference range levels, as normal or lowthere was no significant difference of grip strength and BMD levels between groups. The grip strength of the patients with panhypopituitarism were significantly low.
Conclusion
The muscle strength of the hypogonad patients are lower than healthy population but the measured low testosterone levels of the patients under regular replacement therapy may notcorrelate directly with muscle strength.

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AEP833

First in man study of oral native testosterone in hypogonadal men shows physiological testosterone levels in fed and fasted state

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Introduction
Current testosterone replacement therapies have limited acceptability: gels can be messy and risk inadvertent dosing of others; injections are painful; and oral testosterone undecanoate (TU) delivers variable testosterone levels, requires concurrent ingestion of a fatty meal and may produce supraphysiological dihydrotestosterone (DHT) levels[1]. We present the first human trial of an oral native testosterone preparation formulated to deliver testosterone irrespective of food intake.
Aim
To compare the pharmacokinetics of DITEST (Diurnal Ltd Cardiff, UK) to an oil based oral TUformulation (Andriol Testocaps, MSD, UK) and explore the effect of food on DITEST bioavailability.
Methods
Single centre, phase 1b study of DITEST in 25 adult males with hypogonadism, one subject withdrawn after single period and only included in safety analysis (Clinicaltrials.gov: NCT02966652). Part 1 compared the pharmacokinetics of 80 mg TU with 120 mg DITEST after a high fat meal. Part 2 the pharmacokinetics of 200mg of DITEST administered fed and fasted. Results are baseline adjusted.
Results
DITEST showed a testosterone dose response between 120 mg and 200 mg with C_{max} 19.1 and 30.4 nmol/l and AUC (0–10 h) 59.5 and 88.6 h*nmol/l. DITEST 200 mg gave an equivalent C_{max} and AUC(0–10 h) to TU 80 mg: C_{max} 30.4 vs 31.4 nmol/l and AUC (0–10 h) 88.6 vs 102 h × nmol/l. Serum TU levels after dosing with 80 mg testosterone undecanoate were 10-fold greater than the testosterone levels generated by TU. Fed and fasted DITEST had similar pharmacokinetics C_{max} 26.5 vs 30.4 nmol/l, AUC (0–10) (87.0 vs 88.6). Both dose strengths of DITEST resulted in lower levels of DHT than TU 80 mg; C_{max} 2.9 [120 mg DITEST] vs 4.5 [200 mg DITEST] vs 6.7 [80 mg TU] nmol/l and AUC (0–10) (11.0 [120 mg DITEST] vs 16.7 [200 mg DITEST] vs 36.3 [80 mg TU] h × nmol/l). There was one serious adverse event (urinary retention) during TU dosing. There was no emerging safety concern.
Discussion
Administration of DITEST in fed and fasted states provides similar testosterone and DHT exposure. TU levels were much higher than testosterone levels suggesting a large proportion of testosterone undecanoate was not converted to testosterone. Compared to published literature on a self-emulsifying formulation of TU at 200 mg, DITEST at 200mg provides a similar testosterone C_{max} and no requirement for a fatty meal[1].
Conclusion
DITEST is an oral native testosterone formulation with anticipated advantages over current oral therapy of dosing without food and less risk of high DHT levels compared to TU therapy.
Reference
1. Yin AY *et al.*, *J Androl* 2012 **33** 190–201.
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AEP834

Vaginal bleeding and spotting in transgender men after initiation of testosterone therapy: A prospective cohort study (ENIGI)
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Background
Persistent vaginal bleeding can be psychologically stressful and incongruent with gender identity in transgender men (assigned female at birth with male gender identity). Previous studieshave cross-sectionally described amenorrhea in cohorts of transgender men on intramuscular or subcutaneous testosterone injections. It remains uncertain which testosterone preparations most effectively suppress vaginal bleeding and when amenorrhea occurs after testosterone initiation. This study investigates the clinical effects of various testosterone preparations on vaginal bleeding and spotting in transgender men.
Methods
This prospective cohort study was part of the European Network for the Investigation of Gender Incongruence (ENIGI). Data on the persistence (yes/no) and intensity (continuous scale) of vaginal bleeding and spotting, serum sex steroid levels and body composition were prospectively and cross-sectionally assessed in 267 transgender men during a three-year follow-up period, starting at the initiation of various testosterone preparations. Testosterone therapy was aimed at male serum testosterone levels.
Results
After three months of testosterone, 17.9% of transgender men reported persistent vaginal bleeding and 26.8% reported spotting. The percentages reporting vaginal bleeding and spotting decreased over the first year of testosterone (bleeding 4.7% and spotting 6.9% at 12 months, respectively), with no participants reporting vaginal bleeding or spotting after 18 months of testosterone. Factors associated with vaginal bleeding or spotting included lower serum testosterone levels and being on testosterone gel, as compared to injections (e.g., esters or undecanoate preparations). If vaginal bleeding persisted, starting progestogens at three months resulted in a decrease in the intensity of vaginal bleeding and spotting.
Discussion
Testosterone therapy aimed at male physiologic ranges will result in cessation of vaginal bleeding and spotting in the majority of transgender men within three months. If not, serum testosterone levels should be measured and testosterone dose adjusted to achieve serum testosterone levels in the physiologic male range. Adding a progestin can be considered after three to six months if bleeding persists. Providers should be aware that cessation of bleeding can be more difficult to achieve in transgender men with lower serum testosterone levels or those on testosterone gel.
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AEP835

Autoimmune characteristics in women with addisons disease and primary ovarian insufficiency
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Background
In women with autoimmune primary adrenal failure (AD) there is a high prevalence of autoimmune primary ovarian failure (POI). Whether the oophoritis is caused by an unknown ovary-specific autoantibodyor cross-autoimmunity with steroid hormone producing cells in the adrenal cortex is unknown. Autoimmune POI can also affect women without AD. Autoantibodies against steroidogenic enzymes are useful diagnostic markers in AD but are of uncertain value in idiopathic POI.
Aim
To compare the prevalence of steroidogenic autoantibodies in AD women with and without autoimmune POI to women with idiopathic POI.
Materials and methods
In this retrospective cross-sectional trial we identified 484 women with AD, using data from the world's largest Registry of Organ Specific Autoimmune Diseases (ROAS).POI was diagnosed based the registry's clinical and biochemical information and further validated using data from The Norwegian Prescription Database. The autoimmune status was evaluated with immunological methods of autoantibody detection against 21-hydroxylase (21 OH), side-chain cleavage enzyme (SCC), NALP5 and 17-hydroxylase (17 OH). Twenty-two women with idiopathic POI were also included.
Results
The prevalence of POI in the AD cohort was 9.1% (44/484). The AD women with POI where youngerwhen diagnosed with AD (30.9 ± 14.0 vs 36.7 ± 15.1 years) and had a subsequently longer AD disease duration (27.7 ± 15.2 vs 21.0 ± 15.5 years).More than half of AD women with POI had ≥3 positive autoantibodies. Autoantibodies against 21 OH were detected in all AD women with POI (100%) and 439 of 408 (93%) AD women without POI. SCC were positive in 35 of 44 with POI (80%) and 61 of 396 (15%) without POI. In women with idiopathic POI, only two of 22 women had positive SCC and none had detectable autoantibodies towards 21OH/NALP5/17OH.
Conclusion
POI is common in AD, and AD women have a higher frequency of positive steroidogenic autoantibodies. In these women, SCC seems to be the most specific marker for autoimmune POI. However, the prevalence of steroidogenic autoantibodies in idiopathic POI is low, suggesting either non-autoimmune cause or highlighting the need for an ovary-specific biomarker for autoimmune oophoritis.
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AEP836

Early menopause is associated with increased risk of arterial hypertension: A systematic review and meta-analysis

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Objective
Menopausal transition has been associated with an increased risk of cardiovascular disease (CVD), mainly attributed to atherogenic dyslipidaemia, central obesity and insulin resistance. Whether arterial hypertension (AH) also contributes to menopause-associated CVD is currently unknown. The aim of this study was to systematically investigate and meta-analyze the best available evidence regarding the association between early menopause (EM) and AH risk.
Methods
A comprehensive search was conducted in PubMed, CENTRAL and Scopus databases, up to January 20th, 2020. Data were expressed as odds ratio (OR) with 95% confidence intervals (CI). The I2 index was employed for heterogeneity.
Results
Ten studies were included in the quantitative analysis (273.994 postmenopausal women, 76853 cases with AH). Women with EM (age at menopause <45 years) were at higher AH risk compared with those of normal age at menopause (>45 years) (OR 1.10, 95% CI 1.01–1.19, $P=0.03$; I^2 79%).
When women with POI were compared with those of normal menopausal age (five studies, 192.219 women), the association between POI and AH risk was not significant (OR 1.14, 95% CI 0.95–1.37, $P=0.17$; I^2 58%). Furthermore, when sensitivity analysis was restricted to studies ($n=8$) in which participants were matched for age or BMI or smoking, the direction or the magnitude of the effect observed did not changed (OR 1.13; 95% CI, 1.00–1.29; $P=0.05$). This was also the case after restricting analysis to studies ($n=2$) matched for ever use of menopausal hormone therapy or oral contraceptives (OR 1.26; 95% CI 1.05–1.52; $P=0.01$).
Conclusions
Women with EM have an increased risk for AH compared with those of normal age at menopause.

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AEP837

Multicentre performance evaluation of the new, fully automated Elecsys ASD immunoassay and determination of reference ranges

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Background
Androstenedione (ASD) levels are used to assess androgen production, adrenal gland and ovarian/testicular function, and diagnosis/monitoring of patients with hyperandrogenism from suspected cortisol-related enzyme deficiencies. According to international diagnostic guidelines, ASD can confirm biochemical hyperandrogenism in suspected polycystic ovary syndrome (PCOS) when total/free testosterone are not elevated. The Elecsys ASD assay (Roche Diagnostics) is a competitive electrochemiluminescence immunoassay for in-vitro quantitative determination of ASD in human serum/plasma. We evaluated the performance of this new, automated assay versus an ASD isotope dilution-liquid chromatography-tandem mass spectrometry (ID-LC-MS/MS) candidate reference method, and determined reference ranges in different clinical cohorts.
Methods
Elecsys ASD assay performance (cobas e 602/cobas e 801 analysers) was evaluated at three sites in Germany/Spain; method comparison was performed internally by Roche Diagnostics; reference ranges were determined at two sites in Germany. Repeatability and intermediate precision were assessed according to CLSI EP05-A3, using three control levels and five human serum pools ($n=75$ each) covering the assay measuring range (0.15–10.00 ng/ml); one run per day for 5 days. Method comparisons versus commercially available immunoassays (IMMULITE ASD [Siemens] and LIAISON ASD [DiaSorin]) and an ID-LC-MS/MS candidate reference method were conducted using 421 serum samples covering the Elecsys ASD assay measuring range; Passing-Bablok regression and Pearson's correlation were calculated. Reference ranges were determined in five clinical cohorts using samples from several sites/vendors: apparently healthy children (≤8 years [US vendor]); apparently healthy women with proven fertile cycle (US, 22–37 years [Trina Bioreactives AG, USA; Roche Wellness Center, USA]; EU/ROW, 18–37 years [UZ Brussel, Belgium; University Hospital Leipzig, Germany; Practice Dr Rohsmann, Germany]); apparently healthy men (≥18 years [Bavarian Red Cross, Germany]); post-menopausal women (55–70 years [NUVISAN GmbH, Germany]); and women with PCOS (18–45 years [Medical University of Graz, Austria]).
Results
Repeatability and intermediate precision CVs across all sites were 2.01–3.91% and 2.43–4.30%, respectively (mean ASD concentrations 2.23–9.92 ng/ml). The Elecsys ASD assay showed poor correlation with IMMULITE ASD (slope=0.459; $r=0.856$; $n=320$), moderate correlation with LIAISON ASD (slope=0.625; $r=0.984$; $n=327$), and very good correlation with ID-LC-MS/MS (slope=1.040; $r=0.996$; $n=332$). Reference ranges (5th–95th percentiles): apparently healthy children ($n=140$), <0.150–0.382 ng/ml; apparently healthy women ($n=84$), 0.490–1.31 ng/ml; apparently healthy men ($n=138$), 0.355–1.26 ng/ml; post-menopausal women ($n=140$), 0.208–0.990 ng/ml; women with PCOS ($n=125$), 0.756–3.03 ng/ml.
Conclusion
The Elecsys ASD assay demonstrated excellent precision and very good correlation with ID-LC-MS/MS. Reference ranges were established to support results interpretation in routine clinical practice.

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AEP838

Modifications of autoimmune markers in women with infertility and autoimmune thyroiditis

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Introduction
Thyroid hormones affect sex hormone metabolism and reproductive function in women. Infertility in women with autoimmune thyroiditis is more difficult to treat than in women with normal thyroid function. On the other hand, immune factors are dependent on exogenous and endogenous factors, interrelated with hormones and are important regulators of fertility, autoimmune reactionsand can lead to infertility and increase the risk of pregnancy complications and miscarriage.
The aim of the study
To determine the features of changes of autoimmune markers in women suffering from infertility and autoimmune thyroiditis.
Materials and methods
The study was conducted through detailed analysis of medical records of 32 women, which were diagnosed with infertility of unexplained genesis and autoimmune thyroiditis. The control group consisted of 30 women with tubal genital infertility. The comparison group consisted of 30 healthy women. Determination of the indicators of thyroid function (thyroid-stimulating hormone, total thyroxine, free thyroxine, total triiodothyronine, free triiodothyronine, antibodies to thyroperoxidase (APO), antibodies to thyroglobulin (ATG)) was conducted by ELISA. Autoimmune markers: antisperm antibodies, antinuclear antibodies (ANA), Ro/SS-A, La/ss-B, CENP-B, Scl-70, dsDNA, Jo-1, MPO, PR3, AMA and Sm were determined out by Western Blot method.
Results
It should be noted that among all women who came to the clinic complaining about infertility for the first time, 11.34% were diagnosed with autoimmune thyroiditis. This diagnosis was the most common among all autoimmune disorders in infertile women compared to an increase in antisperm antibody levels – only 1.3% were observed, and to the proportion of all other autoimmune diseases combined – was less than 10%. The following autoimmune markers showed significant changes in women of the study group:

APO titers increased in the range of 2.4–11.2 times (P <0.001), ATG – increased in the range of 1.7–8.3 times (g <0.001), ANA – growth in the range from 1: 100 to 1: 1000 (P <0.001) compared to the control. We did not reveal significant changes of the rest of the autoimmune markers that were under the study.
Conclusion
Thus, a significant increase in the levels of thyrospecific and antinuclear autoantibodies in women with infertility on the background of autoimmune thyroiditis were revealed, which may cause fertility disorders and the search for new methods of solvation of this problem is necessary.
Keywords: infertility in women, autoimmune thyroiditis.
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AEP839

The diagnostic value of antimullerian hormone in polycystic ovary syndrome among Tunisian women: A case-control prospective study

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Introduction
Polycystic ovary syndrome (PCOS) is a common endocrine disorder. The presence of polycystic ovarian morphologyis usually confirmed by ovarian ultrasound. However, its definition is controversial. The objective of this study was to evaluate the interest of the antimullerian hormone (AMH) in the diagnosis of PCOS, aiming to establish a threshold that would be predictive of PCOS among Tunisian women.
Patients and methods
Sixty-twoyoung women (31 with PCOS and 31 age and BMI matched healthy controls) were recruited in this case-control, prospective, cross-sectional study. All participants had physical examination, ovarian ultrasound and dosage of AMH and testosteronemia.
Results
All patients had clinical and/or biological hyperandrogenism. The mean rate of AMH was 3.6 times higher in patients (7.69 ng/ml) compared to controls (2.12 ng/ml; P < 10–3). The cut-off value for AMH which was best correlated with PCOS was 3.41 ng/ml (sensitivity = 96.8%; specificity = 90.3%; AUC = 0.977). A significant positive correlation between AMH and antral follicular number, and between AMH and testosteronemia was found. A significant negative correlation between AMH and age was also found. We noted no significant association between AMH and BMI. The most common PCOS phenotype was the A one combining the three diagnostic criteria for PCOS (52%). This phenotype had the highest rate of AMH.
Conclusions
Our results suggest that AMH may be a reliable biomarker in the diagnostic of PCOS. It may replace ovarian ultrasound if it is not available, inconclusive and/or in the absence of a qualified operator. The threshold of 3.41 ng/ml would be appropriate for Tunisian hyperandrogenic patients.
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AEP840

Hormonal profile of menopausal women receiving androgen replacement therapy: A meta-analysis

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Background
Ovarian and adrenal aging leads to a progressive decline in androgens levels and deleterious effects on the quality of life. Despite this, specific hormone replacement is not routinely recommended in the management of women with a physiological or pathological decline in their production, mainly due to the lack of long-term follow-up safety data.
Aim of the study
To evaluate and summarize the existing data about hormonal profile changes in menopausal women receiving androgen replacement treatments, considering all available androgens formulation and regimens.
Methods
The literature search was conducted to identifyall randomized clinical trials and case-control studies evaluating hormonal effects of exogenous administration of any molecule with androgenic action in post-menopausal women published in English language until May 2018 (PROSPERO registration ID: CRD42018099414).
Results
Fifty-threepapers were included in the analysis, accounting for 83 trials. Androgen administration increases testosterone serum levels (2159 treated women vs 2246 controls, P<0.001), regardless of the molecule used. Similarly, an increase of dehydroepiandrosterone (DHEA) and DHEA-sulfate serum levels was observed (P<0.001 and P<0.001, respectively), with a concomitant reduction in sex hormone binding globulin (SHBG) levels (P<0.001). However, the estrone (E1) and estradiol (E2) increase is evident only when DHEA is administered (P<0.001 and P<0.001, respectively), and not when testosterone (P=0.120 and P=0.690, respectively) or androstenedione (P=0.400 and P=0.540, respectively) where chosen.
Conclusion
Whatever androgen formulation we choose in postmenopausal women, the final result is a rise in testosterone serum levels. However, DHEA regimen shows a combined estrogenic activity. This peculiar action is crucial when choosing the best possible treatment for each patient individually taking into consideration if potential benefits outweigh the risks.
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AEP841

Androgens in women – the methods for their determination

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Four androgens are routinely measured in women: dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, and testosterone. The diagnosis of hyperandrogenemia in women is accompanied by many difficulties. One of them is the method used to measure androgens in the laboratory. In most laboratories, androgens are determined using various immuno-analytical methods. Recently, gas or liquid chromatography combined with mass spectrometry have begun to be use. These instrumental techniques should be prefered for androgen mesurement in women due to their low circulating levels. Another difficulty with androgen laboratory assays are reference ranges, which can not just be automatically taken from other references but should be tested and confirmed in each laboratory. We determined our laboratory reference range for DHEA, androstendione and testosterone quantified using newly developed LC-MS/MS method in fertile, postmenopausal and pregnant women and their newborns in plasma. DHEAS was also estimated (radioimunoassay). Moreover, we have calculated biologically available testosterone. SHBG and albumin (calculation of biologically available testosterone) and LH (phase of cycle) were measured using immunoanalysis. Reference ranges were calculated based on the 2.5th–97.5th percentiles of measured data. For calculating ranges in fertile women, 220 healthy woman samples were analyzed (average age 29.8 years). Dividing into four phases of the menstrual cycle was performed based on the day of the cycle and LH levels. Calculating of reference ranges in healthy postmenopausal woman was performed by analyzing 97 plasma samples (average age 58 years). Samples from 142 healthy women (average age 31.41 years) with physiological gravidity at the 37th week, during the first period of spontaneous labor, and from newborn mixed cord blood divided in two group according the fetal sex were used for calculating reference ranges. All probands were not using any medications, had no clinical signs of hyperandrogenemia. Androgens levels of fertile women change during menstrual cycle with higher levels in ovulation phase (for example: follicular phase testosterone: 0.10–1.53 nmol/l and ovulation phase testosterone: 0.28–2.02 nmol/l).Pregnant women at the 37th week carrying male fetus have higher levels of androgens (testosterone: 0.73–5.79 nmol/l)than pregnant women carrying female fetus (testosterone: 0.99–5.07 nmol/l). Using

LC-MS/MS methods and determination of own reference ranges for these androgens could improve the diagnostics of hyperandrogenemia in women.
Acknowledgments
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AEP842

Evaluation of erectile dysfunction leading to a diagnosis of myotonic dystrophy

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Erectile dysfunction is a common complaint of men with hypogonadism. We present the case-history of a 42-year-old man who complained of erectile dysfunction for four years. Previous paternity was mentioned in his past medical history. On clinical examination his appearance was eunuchoid with frontal balding, reduced chest hair and lipomastia. Bilateral ptosis was also noticed and after being questioned the patient admitted that he had surgically repaired eyelid ptosis one year ago. His testes measured 8 ml each. Investigations revealed hypergonadotrophic hypogonadism (testosterone 1.88 ng/ml (normal range: 2.5–8.36) FSH 35 mIU/ml (nr: 1.5–12.4) LH 26.7 mIU/ml (nr: 1.7–8.6)) as well as elevated liver enzymes (SGOT: 49 IU/l, SGPT 65: IU/l, γ-GT: 205 IU/l) and CPK: 416 IU/l. Genetic analysis confirmed the presence of an-over 150 times-expansion of CTG repeat in the dystrophia myotonica protein kinase (DMPK) gene, a finding consistent with myotonic dystrophy type 1. After diagnosis was confirmed, the patient was examined for endocrinopathies known to be related to DM1. Thyroid function tests, PTH and cortisol levels were normal and the HOMA-IR level was 2.5. This case report highlights the need of thorough examination of all patients presenting with erectile dysfunction even for rare causes of hypogonadism.

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AEP843

Hyperandrogenism in a postmenopausal woman secondary to an androgen secreting steroid cell tumor of the ovary

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Introduction
Androgen secreting neoplasms of the ovary are rare and usually show autonomous secretion. Steroid cell tumors of the ovary represent less than 0.1% of all ovarian tumors and are a subgroup of sex cord-stromal tumors. In most cases, patients present with androgenic clinical features.
Case report
A 58-year-old woman complained of rapid onset of androgenic alopecia, excessive hirsutism and clitoromegaly. Endocrine assessment showed high levels of testosterone 293 ng/dl (4–60), with normal levels of other androgens. Abdominal magnetic resonance revealed a solid nodular lesion of the right ovary with 13×14 mm suggestive of a sex cord-stromal tumor. The patient underwent bilateral hystero-ophorectomy. The histopathology diagnosis was steroid cell tumor, not otherwise specified. Four months after surgery, hormonal evaluation demonstrated normal plasma testosterone levels and the patient refers some regression of androgenic features.
Conclusion
The rapid onset of virilization in a post-menopausal woman should lead to a search for an androgen-secreting ovarian or adrenal tumor. Surgery is the main treatment for these tumors. Although steroid cell tumors of the ovary are generally benign, there is a risk for malignant transformation and little is known about their behavior, so it is important to keep these patients under surveillance.

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AEP844

Severe hyperandrogenaemia and unusually large polycystic ovaries: A case report

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Introduction
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of young women and depending on the diagnostic criteria, it affects 6% to 20% of reproductive aged women. PCOS is also the most common cause of hyperandrogenism in young women with the theca cells of the ovary being the source of androgen excess. PCOS is rarely associated with severe hyperandrogenaemia and atypical features such as rapid progression, presence of virilization or very high Testosterone/ androgen levels should prompt comprehensive evaluation to exclude a sinister underlying cause.
Case report
A 19-year-old Caucasian female with background of autism presented with secondary amenorrhoea, moderate acne and recent onset mild hirsutism. Examination revealed a modified Ferriman-Gallwey score of 12, central obesity with BMI 33.9 kg/m^2 and no signs of Cushing's syndrome. Biochemical workup revealed severe hyperandrogenaemia with a Testosterone 4.9 nmol/l (<1.8), low SHBG 8.2 nmol/l (26–110) and a very high free androgen index of 59.7. Androstenedione was also significantly high 19.5 nmol/l (0.9–7.5). DHEAS was mildly elevated 11.3 µmol/l (1.8–10). 17-OHP was normal. In order to distinguish ACTH-dependent hyperandrogenism from other causes of hyperandrogenism, 1 mg overnight dexamethasone-suppression test was performed which suppressed Testosterone to less than 40% (from 3.8 nmol/l to 2.6 nmol/l); Androstenedione suppressed from 24.8 nmol/l to 12.6 nmol/l and there was enough Cortisol suppression to 13 nmol/l, excluding Cushing's syndrome. She refused a transvaginal ultrasound scan of the pelvis and had MRI of the pelvis and adrenals which excluded ovarian and adrenal neoplasm; imaging features were highly suggestive of PCOS with bilateral very large ovaries (right ovary measuring 50 cc and left ovary measuring 32 cc in volume) containing multiple (at least 20–22) small sub-centimetre sized follicles.
Conclusion
This case highlights a rare presentation of a common disorder and is unusual in that the high concentration of androgens and very high free androgen index were not associated with a sinister ovarian or adrenal pathology. Mild hirsutism despite severe hyperandrogenaemia might be explained by a relatively shorter duration of exposure to androgens, low intrinsic sensitivity of her hair follicles to androgen action or reduced local 5-alpha-reductase activity. Although her presenting features were relatively mild, significantly elevated androgens and recent onset hirsutism raised concern for non-PCOS pathology requiring suppression testing and imaging for accurate diagnosis and appropriate treatment.

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AEP845

The effect of diabetes mellitus on age at natural menopause: A systematic review

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Introduction
Menopause marks a period of significant changes on hormones and on the women's lifestyle, which can interfere with their subsequent health. Menopause marks not only the end of the woman's reproductive life, but also the upcoming associated risks for many morbidities, as well. The increasing prevalence of diabetes (either type 1 Diabetes Mellitus (T1DM) or type 2 Diabetes Mellitus (T2DM) renders a necessity to investigate its effects on women's age of menopause.
Aim
The aim of this review was to systematically evaluate all the available literature on how diabetes affects women's age at menopause.

Method
An extensive literature search was conducted through electronic databases (Pubmed, Scopus, Cinahl and Medline) with the terms of 'age', 'menopause', 'premature' and 'diabetes mellitus', till December 2019. The search yielded 116 results, 11 of which met the inclusion criteria.
Results
Five of the included studies examined the correlation of T1DM with the age of menopause and six studies of T2DM, respectively.
In the EPIC study, menopause occurred significantly earlier among women with T1DM (WT1DM). In a sample of Finnish WT1DM the age at menopause was reported to be the same as in general population. In the OVADIA study, a similar menopausal age was reported in both groups. In the DCCT/EDIC cohort, WT1DM appeared a similar age at menopause onset compared to the average age of menopausal women in the U.S. In the FAD study, a younger age at menopause, among WT1DM was demonstrated.
In the SWAN study, women with T2DM (WT2DM) experienced their final menstrual period in a significantly earlier age than women without diabetes. Moreover, in an Indian population, the average age of menopause among diabetic women was much younger than in non-diabetic. In a Latin American study, the risk of being postmenopausal in WT2DM aged 40–44 years was found to be nearly three times higher than in those without. In contrast, in a study of Mexican WT2DM was found that they experienced a similar menopausal age with non-diabetic women. Likewise, in the EPIC study no relationship between diabetes and age at menopause was observed. Finally, the age of menopause onset in Nigerian WT2DM was found similar to the age of commonly reported in Nigerian women population.
Conclusion
The findings of this systematic review remain inconclusive regarding the effect of diabetes on age at menopause. It is important to verify that diabetes could affect the age of menopause, through future well-organized multicenter studies.

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AEP846

Gonadal dysfunction is associated with severity of disease in men with myotonic dystrophy type 1

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Background
The myotonic dystrophy type 1 (DM1) or Steinert disease is the most common inherited, autosomal dominant neuromuscular disorder in adult. The gonadal dysfunction has been known for many years in DM1 men with description of bilateral testicular atrophy but the factors influencing the different profiles of gonadal dysfunction, and their natural evolution are not clearly established. The purpose of this study was to determine the profiles of gonadal function on men affected by DM1 followed in a single reference center and to analyse the factors influencing this gonadal profile.
Results
in the whole population, the mean age of the 75 patients was around 40 years, 57% of them being younger than 40 years old. More than half (53.3%) of these 75 patients had an adult form of the disease. The median number of CTG repeat was 450 (200–650). Forty percent of the patients had normal gonadal status. Sixty percent of patients had alteration of hormonal results. Thirty-seven percent of patients had isolated exocrine testicular lesion and 22% of patients had hypogonadism. This last, hypogonadal patients, had higher BMI and had more metabolic disorders than in patients with exocrine testicular failure or normal gonadal status. They had also more severe disease (evaluated by the number of triplets) and more severe muscular involvement (evaluated by MIRS score) than other patients, regardless of their age. Also paternity was significantly lower in hypogonadic patients than in other patients. Testosterone (t) and testosterone/SBP ratio (t/S) were inversely correlated with the age of patients (t: $r=-0.32$, $P=0.005$; t/S: $r=-0.49$, $P<0.001$) and with the MIRS score (t: $r=-0.37$, $P=0.001$; t/S: $r=-0.32$, $P=0.006$). There was not correlated with paternity and number of CTG repeats.
Conclusion
In this cohort of 75 DM1 patients aged arount 40, we observed a high prevalence of primary testicular failure with one patient out of 5 with hypogonadism. This gonadal dysfunction was significantly correlated to the number of CTG repeats, the severity of muscle involvement assessed with the MIRS score, and the metabolic syndrome regardless of the age of the patients.
The efficacy of androgen therapy on metabolic and muscular syndrome, and its acceptability by patients need to be studied, as well as the effect of an improvement of metabolic status or muscular strength through rehabilitation that might also have beneficial effects.

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AEP847

Psychological status and quality of life in men with hypogonadism and type 2 diabetes mellitus, receiving testosterone replacement therapy

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It is known that the presence of type 2 diabetes mellitus (T2DM) deteriorates the psychological status of patients, but its combination with a deficiency of testosterone (T) in men is not well studied. The aim of this work was to study the effect of T replacement therapy (TRT) on the levels of anxiety, depression, symptoms of androgen deficiency, diabetes and quality of life in men with T2DM and functional hypogonadism.
Materials and methods
We examined 90 men with T2DM and a T deficiency (mean age 51.5±6.3 years), which were divided into 2 groups: 1–40 patients who received TRT using transdermal T-gel (Androgel 50 mg/day) for 9 months and standard hypoglycemic therapy and 2–50 patients who were not assigned to TRT and received just antidiabetic drugs. Patients underwent clinical and psychological examinations, such as questionnaires HADS, aging male symptoms (AMS), symptoms of diabetes (DSC) and quality of life (SF-36). Statistical analysis of the data was carried out using the Wilcoxon test for time-depended parameters and Mann-Whitney U test for two independent groups using the Statistica software package (StatSoft 10).
Results
Analysis of the AMS questionnaire in men who received TRT revealed a significant ($P=0.003$) decrease in the total score of androgen deficiency symptoms from 38.5 [35; 46] to 30 [24; 39]. The diabetic symptoms according to DSC questionnaire also were decreased: the psychological scale by 0.75±0.04 points ($P=0.04$), manifestations of hyperglycemia by 0.5±0.09 points ($P=0.04$) and neuropathy scale by 0.6±0.03 ($P=0.02$) points. Moreover, the anxiety levels were significant decreased 1.8-fold ($P<0.001$) and depression level – 2-fold ($P=0.001$) in the 1st group. The quality of life according to SF-36 questionnaire were significant improved ($P<0.01$) in the physical functioning, general health, vitality, social functioning, and role-emotional scales compared to baseline in patients receiving TRT. In the control group no significant changes occurred.
Conclusion
The appointment of TRT in men with T2DM not only reduces the symptoms of androgen deficiency and diabetes, but also significantly decreases levels of anxiety and depression, which improve the quality of life in these patients.
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AEP848

Serum inhibin B level distinguishes congenital hypogonadotropic hypogonadism from constitutional delay of growth and puberty in males: A systematic review and meta-analysis

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Objective
The distinction between constitutional delay of growth and puberty (CDGP) and congenital hypogonadotropic hypogonadism (CHH) in males with delayed puberty is difficult but important for timely treatment. We aimed to summarize the sensitivity and specificity of serum inhibin B (INHB) level in distinguishing CHH with CDGPin boys.
Methods
Studies in the PubMed, EMBASE and Cochrane Library databases were systematically searched from the date of database inception to November 10, 2019.Studies incorporating INHB discriminating between CHH and CDGP were included. The quality assessment of diagnostic studies

2 (QUADAS-2) instrument was used to assess the quality of the included studies. Meta-Disc version 1.4. was used to calculate the sensitivity, specificity, summary receiver-operating characteristic (sROC) curves, and area under the curve (AUC).

Results

Six studies, comprising 328 patients (87 CHH vs 241CDGP), were eligible for this meta-analysis. For the differential diagnosis between CHH and CDGP, INHB measurement had a good diagnostic accuracy with a pooled sensitivity of 92%, specificity of 91%, pooled AUC of 0.9616. INHB performed well especially in CHH and CDGP boys with severe puberty deficiency (testes volume ≤3 ml), with sensitivity of 92%, specificity of 98% and AUC of 0.9956.Subgroup analysis weredisplayed in Table 1.

Table 1 Summary results of subgroup analysis for INHB in the diagnosis between CHH and CDGP.

Categorical variable	No. of studies	Sensitivity 95% CI	I^2(%)	Specificity 95% CI	I^2(%)
Testes volume(ml)					
≤3	3	0.92 (0.79–0.98)	67.4	0.98 (0.90–1.00)	22.3
≤4	3	0.93 (0.81–0.99)	0.00	0.85 (0.78–0.91)	53.7
≤6	2	0.90 (0.74–0.98)	0.00	0.96 (0.89–0.99)	85.6
Study design					
Prospective	4	0.93 (0.82–0.98)	51.4	0.99 (0.95–1.00)	23.7
Retrospective	4	0.91 (0.81–0.97)	0.00	0.86 (0.80–0.91)	38.2
Methodological quality					
Low risk	5	0.92 (0.83–0.97)	36.1	0.97 (0.93–0.99)	54.0
Not low risk	3	0.91 (0.80–0.98)	0.00	0.84 (0.76–0.90)	15.3

Conclusions

INHB has an excellent diagnostic performance in differentiating CHH from CDGP, retaining both considered sensitivity and specificity. INHB has better diagnostic efficacy in boys with severe puberty deficiency (testes volume ≤3 ml). (Grant/Award Number: 201604020090, Guangzhou Science and Technology Programme)

Keywords: Inhibin B, congenital hypogonadotropic hypogonadism, constitutional delay of growth and puberty, meta-analysis.

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AEP849

Aminoacidic residues discriminating human choriogonadotropin (hCG) and luteinizing hormone (LH) binding to the human receptor (LHCGR)

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The human luteinizing hormone (LH)/choriogonadotropin (hCG) receptor (LHCGR) discriminates its two hormone ligands. LHCGR differs to the murine receptor (Lhr) in aminoacid residues potentially involved in qualitative discerning of LH and hCG, the latter absent in rodents. We aim to identify LHCGR residues involved in hCG/LH discrimination, indicating evolutionary determinants of human LH/hCG endocrine system. After comparing the LHCGR and Lhr sequences, we developed eight *LHCGR* cDNAs carrying 'murinizing' mutations (R247T; T48R; S149F; I83S; A57T; E270V; N35D and V37A; K225S and T226I) assumed to be interacting specifically with LH, hCG or both. HEK293 cells expressing a mutant or the wild-type receptor were treated by pM-μM LH or hCG concentrations and the kinetics of cAMP and pERK1/2 activation was analysed by BRET. A Lhr-like response was obtained in cells expressing LHCGR carrying the A57T mutation as hCG is more potent than LH in inducing both cAMP (LH EC_{50}=0.7±0.2 nM vs hCG EC_{50}=0.1±0.03 nM; Mann-Whitney's *U*-test; $P<0.05$; $n=4$; means±S.E.M.) and kinetics of pERK 1/2 activation (Kruskal-Wallis test; $P<0.05$; $n=8$). The E270V mutation located in the LHCGR hinge region decreased of 2.5 times the LH, but not hCG potency in inducing cAMP production than the wild-type (LH EC_{50}=2.8±1.4 nM vs LH EC_{50}wild-type=1.1±0.3 nM; hCG EC_{50}=0.2±0.04 nM vs hCG EC_{50}wild-type=0.15±0.03 nM; $n=4$; means±S.E.M.), suggesting this extracellular portion of the receptor is involved in LH-specific recognition. LHCGRs carrying K225S, T226I or R247T mutations mediate similar cAMP (LH EC_{50}=0.6±0.2 nM vs hCG EC_{50}=0.11±0.1 nM and LH EC_{50}=5.6±0.4 nM vshCG EC_{50}=0.4±0.02 nM; Mann-Whitney's U-test;$P>0.05$; $n=4$) and pERK1/2 response to LH and hCG (Kruskal-Wallis test; $P>0.05$; $n=8$). Via 'murinization' of LHCGR, we identified key aminoacids falling within the extracellular region of the receptor interacting with the hormone L2-β loop, which might be crucial for discriminating the two human gonadotropin ligands. We found human-specific determinants of the LH/hCG system evolution.

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AEP850

An investigation into the age and developmental stage related association between plasma concentrations of leptin and growth hormone, linear growth velocity, body mass index and body surface area in boys between the ages of 1 and 20 years

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Puberty, one segment of a larger developmental continuum in humans, is characterized by major transformations in body such as highest growth, sexual development and distribution of fat in different body regions. Leptin is regarded as an essential adipokine that regulates intake of food, expenditure of energy and body fat mass. It is well known that alterations in nutritional states markedly influence growth hormone (GH) secretion, which in turn regulates linear growth, muscle strength, body fat mass and lipid metabolism. Also, leptin affects bone metabolism via direct signaling from the brain. Leptin decreases cancellous bone, but increases cortical bone, which is a mechanism for increase in bone size. Leptin may also act directly on bone metabolism via a balance between energy intake and the IGF-I pathway. Therefore, this study was designed to examine possible associations between plasma concentrations of leptin and GH, linear growth velocity (LGV), body mass index (BMI) and body surface area (BSA) at different ages and developmental stages in boys between 1 to 20 years (27 boys/age group). The concentrations of leptin and GH were determined using specific ELISA, while LGV, BMI and BSA were calculated using formulae for each age/stage group. Data were analyzed using Student's *t* test, ANOVA and Pearson correlation r. Our results showed a positive correlation between plasma leptin and GH levels at 3rd, 6th, 8th, 10th, 12th, 16th to 18th and 20th year of age and at infancy, early puberty and late puberty. The leptin levels and LGV were positively correlated at 3rd, 4th, 8th to 10th, 12th and 16th to 18th year of age indicating correlation at early puberty and late puberty. Moreover, the leptin levels and BMI were positively correlated at 1st, 4th to 6th, 8th, 9th, 12th, 15th and 18th to 20th year of age demonstrating correlation at infancy and early puberty. Likewise, the concentrations of leptin and BSA were positively correlated at 1st, 2nd, 5th through 12th, 19th and 20th year of age showing relationship at infancy, pre-puberty and early puberty. In conclusion, leptin and GH, LGV, BMI and BSA were found to be positively correlated at infancy and early puberty.

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AEP851

Modern approaches to ovulation induction in patients with poor ovarian response

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Background
Aromatase inhibitors have been introduced as a new treatment modality in controlled ovarian stimulation as they were found to elevate follicular sensitivity to gonadotropins.
The purposeof this study was to evaluate whether IVF outcomes will differ between poor responder patients who receive high doses of gonadotropins alone or low doses of gonadotropins with letrozole during ovulation stimulation.
Methods
Patients who underwent *in vitro* fertilization treatment classified as poor responder patients according. Inclusion criteria: patients being aged between 18 and 42 years, having regular menstrual cycles (between 25–32 days), having normal BMI (between 19.3–28.9 kg/m.), having normal hormone levels, having normal endometrium (evaluated with hysteroscopy). Exclusion criteria: chemotherapy and radiotherapy, ovarian surgery in anamnesis. The controlled ovarian stimulation were started on third day of the menstrual cycle. In the I Group, 24 patients were treated with 150 IU gonadotropins in combination with letrozole 5 mg/day for the first five days of the stimulation. In the II Group, 32 patients were treated with 300 IU gonadotropins. Patients were treated with 0.25 mg GnRH antagonist given from stimulation day 6 onwards. When at least three follicles were 18 mm in size, a single dose of 250 µg hCG was injected for follicular maturation. Oocyte retrieval took place for the 34–36 hours after hCG trigger. Oocytes were fertilized by conventional ICSI and cultured until the day of embryo transfer.
Results
Group I and II, there were no statistically significant difference in duration of ovulation stimulation, duration of antagonist use, number of retrieved oocytes, number of transferred embryos, implantation rate, clinical and ongoing pregnancy rates ($P>0.05$). Gonadotropin use was significantly higher in Group II (300 IU gonadotropins) compared to I Group (150 IU gonadotropins in combination with letrozole 5 mg/day), ($P<0.05$).
Conclusion
Using letrozole with low doses of gonadotropins in patients with POR does not improve the pregnancy outcomes compared to high doses of gonadotropins alone. However, the addition of letrozole can make pregnancy outcomes comparable using significantly lower doses of gonadotropins, so may be regarded as an effective adjuvant agent in POR patients.

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AEP852

Headache in patients with polycystic ovary syndrome

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Introduction
Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder among reproductive age women having negative impact on their health, personal and social live. In scientific literature data on headache in PCOS women are scarce.
Aim of the study
To investigate the frequency of headache and its association with metabolic parameters and diet habits in women with PCOS.
Materials and methods
114 PCOS women and 80 healthy control women took part in the study. Body weight, height, blood pressure were measured. Hormones, complete blood count, fasting glucose, fasting insulin and lipid profile tests were performed. Information about headache, nutrition habits and physical activity was collected utilizing qualitative frequency questionnaires.
Results
The mean participants' age was 27.52±3.80 years, the mean BMI was 25.08±6.20 kg/m^2. 65.5% of studied women complained on headache attacks: 68.5% of them were experiencing tension-type headache, 26.0% of them had migraine. PCOS women experienced headache more frequently than control group's women (72.8% vs 55.0%, $P<0.010$). Rate of tension-type headache were higher in PCOS women than in control group (52.6% vs 33.8%, $P=0.009$), rate of migraine didn't differ between groups. PCOS women more frequently stated, that headache affected their professional live (31.6% vs 18.8%, $P=0.046$) and everyday activities (24.6% vs 11.2%, $P=0.020$) than controls.
Overweight and obese PCOS women more frequently experienced headache than normal-weight PCOS women (81.5% vs 61.2%, $P=0.016$). Being overweight or obese increased odds ratio of having headache 2.8 times ($P=0.018$). No difference in headache frequency between healthy overweight and normal-weight women was detected.
Headache rate was lower among PCOS women every day eating whole grain bread and white flour than in PCOS women occasionally eating whole grain bread and white flour (respectively 25.3% vs 48.1%, $P=0.027$ and 15.0% vs 32.1%, $P=0.049$). Headache rate was higher among PCOS women every day eating potatoes than in PCOS women occasionally eating potatoes (18.5% vs 3.4%, $P=0.039$).
Conclusion
PCOS women more frequently have headache affecting professional live and every day activities. Overweight is associated with headache frequency in women with PCOS.

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AEP853

A case of swyer syndrome

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Introduction
Swyer syndrome is caused by abnormal sex differentiation during the embryonic period, resulting in incomplete intrauterine masculinization and undifferentiated gonads associated with a 46, XY karyotype in phenotypic females. They have normal female external genitalia and underdeveloped female internal genitalia. Such patients usually present with primary amenorrhea and delayed puberty but can also have gonadal tumors as adults. The exact incidence is unknown. The syndrome has been estimated to occur in 1 in 80.000 births.
Case report
A 18 years old child, reared as female, born of non-consanguineous marriage, presented to our Out-patient Department with primary amenorrhea with no breast development, but normal pubic and axillary hair. She is the second in her siblings, one elder brother (21 years), two younger (male 16, female 14) all achieved puberty. Her mother had her menarche at age of 15. On systematic enquiry, no symptoms suggestive of any system affection past medical, family, and developmental histories were normal.
Examination
General and systemic examinations were within normal limits; the subject had no stigmata of Turner's syndrome. Weight: 48.5 kg, Height: 149 cm (–2 S.D.), span 156 cm, US/LS ratio 0.8, mid parental height (–1.–2 S.D.).
No breast budding, pubic hairtanner stage 4, External genitalia were normal; there was no evidence of ambiguity.
Investigation
Routine biochemical and hematological investigations were within normal limits. Hormonal evaluations were consistent with primary gonadal failure: FSH 98 mIU/ml (3.5–12.5). LH42.15 IU/l (2.4–12.6), E2 less than 5, T.Testosterone 0.16 ng/dl (0.15–0.8), F.testosterone 2 ng/dl (1–5).
Normal thyroid profile
Bone age by X-ray: 13 years/Abdominal/pelvic US: infantile uterus, absent ovarian tissue replaced by fibrous tissue bilaterally (Pure gonadal dysgenesis). /MRI pelvis: hypo plastic infantile uterus, with absent ovarian Tissue. Karyotype analysis revealed 46XY, without MosaicismA FISH study revealed 95% XY that the proband was positive for SRY region 45% on Y-chromosome. She was started on low-dose continuous estrogen priming, following which she had break through bleeding. She wasthen prescribed combination of estrogens and progestogen to induce cycling bleeding. Multiple psychological counselling sessions were held. Parents werecounselled about the risk of gonadal tumor and were advised gonadectomy but they refused.
Conclusion
This case report calls attention to exclude rare Disorder of Sex Development like Swyer syndrome in a subject with primary amenorrhea, accurate and early diagnosis would allow conservative treatment and appropriate psychological counselling, which reduces emotional trauma and improve patient survival.

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AEP854

Age and developmental stage dependent relationship between thyroid hormones and follicle stimulating hormone, luteinizing hormone, testosterone and inhibin B in boys between the ages of 1 and 20 years

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The maturation of hypothalamo-pituitary-gonadal (HPG) axis causes the onset of puberty, which stimulates the development of secondary sex characteristics and changes in the size and composition of the body. Furthermore, the size of the thyroid gland increases and its function also changes as an adaptation to the requirements of the transformation of child to an adult. It has also been reported that the thyroid hormones including thyroxin (T4) and triiodothyronine (T3) have a facilitative action on the reactivation of the release of GnRH in pulsatile pattern at the time of puberty. In humans, it has been suggested that thyroid hormones affect reproductive functions and fertilizing ability since T3 has been demonstrated to have an essential function in testicular development by controlling the differentiation and proliferation of Leydig and Sertoli cells by binding to Sertoli cells during the development of testes. It has been reported that the proper functioning hypothalamo-pituitary-thyroid (HPT) axis is essential for proper reproductive development in human. The secretion of thyroid hormones is altered under different physiological and pathological conditions including puberty and stress. The current investigation was planned to systematically examine possible associations between plasma concentrations of T3 and FSH, LH, T and inhibin B at different ages and developmental stages in boys between 1 to 20 years of age (27 boys/age group). The concentrations of T3, FSH, LH, T and inhibin B were determined using specific ELISA systems. The data were analyzed using Student's t test, ANOVA and Pearson correlation r. The concentrations of T3 and FSH were positively correlated at 1st-3rd, 7th-12th, 14th, 18th and 19th year of age and at infancy, early, mid and late puberty. Moreover, the concentrations of T3 and LH were positively correlated at 1st, 6th, 9th to 15th, 17th and 19th year of age and at all developmental stages including infancy, pre-puberty, early, mid and late puberty. Similarly, T3 and T concentrations were positively correlated at 1st, 3rd, 6th, 8th to 15th, 17th, 19th and 20th year of age and at all developmental stages. Furthermore, T3 and inhibin B levels were positively correlated at 1st, 3rd-6th, 10th-14th, 18th and 20th year of age and at infancy, pre-puberty, early and mid-puberty. In conclusion, T3 and LH and T levels were found to be positively correlated at all developmental stages from infancy to late puberty, whereas T3 and FSH and inhibin B levels were positively correlated at infancy, early puberty and mid-puberty.

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AEP855

Intensive marathon running: Don't over do it!

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Background
Secondary hypogonadism due to intensive exercise and eating disorders are well documented in females. But there very few reports of secondary hypogonadism due to intensive exercise in male patients.
Case presentation
A 34 year old Caucasian male, presented to our clinic with impaired fertility, lack of libido and increased fatigue. On further enquiry, he mentioned that he had starting running 3–4 yrs. ago, and had been running marathons over the last couple of years since, practicing regularly, runningup to 120 miles/week. He had lost weight over this period. Moreover, he had become a vegan six months ago, and since then lost another one stone in weight. No history of any anabolic steroids or other hormonal misuse. On examination, he had adequate secondary sexual characteristics, including male pattern baldness, and testicles were normal in size bilaterally (25 3 ml). His BMI was 20. Biochemistry results showed hypogonadotropic hypogonadism (with LH 0.7 IU/l, FSH 3.7 IU/l, Testosterone 1.60 mIU/l). Other hormonal results are normal. (9 am Cortisol 453 nmol/l, Free T4 14 pmol/l, TSH 1.51 mIU/l, Prolactin 273 mu/l). MRI scan of Pituitary was normal. Sperm count showed Oligospermia. As fertility was the main concern, in view of above results and with history of intensive training (for Marathons) and also recent dietary change, he was advised to reduce his activity levels, recommended to regain some weight and was also referred to a dietician. At three months review, he had gained 10 kg in weight (and not following Vegan diet) and also reduced the running distance from 120 miles/week to just 40 miles/week and the repeat morning Testosterone has improved to 8.02 nmol/l. After following the same, at 6months review his weight was stable, and still doing only 40 miles/week of running, and the morning Testosterone levels are in normal range at 11. 83 nmol/l. He had mentioned that his Partner is now pregnant. And his libido and erectile dysfunction have improved as well.
Conclusion
Intensive training for Marathon with dietary restriction have caused hypothalamic hypogonadism in this patient, and changes in exercise intensity and duration and weight gain with appropriate dietary changes, has resolved the Hypothalamic amenorrhoea spontaneously.

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AEP856

Effects of perinatal exposure to 4-tert-octylphenol (OP) on brain development and behavior in mice

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Perinatal action of estrogens or aromatizable steroids at the central nervous system level is responsible for brain development. 4-tert-octylphenol (OP) is knows as an endocrine disrupting chemical (EDC) that is widespread estrogenic chemical used in the costumer produces. Thus, we hypothesis that through early contact with the central nervous system, OP could alter the processes affecting behavior. In this study, primary cortical neurons were exposure to OP (10^{-6} or 10^{-8} mol/l) from day *in vitro* 1 to 4 with/without estrogen antiestrogen ICI 182 780. In *in vivo*, we studied the negative impacts of OP on the neuro behavioral development in the offspring generation from OP-supplementation dams (10 or 50 mg/kg on GD9.5 to PND28). Primary cortical neurons were exposure to OP showed increased in the numbers of primary and secondary dendrites. There was no difference in the number ofprimary and secondary axons in OP-treated groups compared to vehicle group. OP-treated groups displayed decreased in the average length both of primary axons and dendrites. Co-treated OP with ICI reversed effect of OP. At 6–8 week-aged, off spring mice from OP-supplementation dams showed limited in acquisition of spatial reference memory and a decreased capability of locating the target in the probe trial of Morris water maze task. In addition, OP-treated groups showed cognition dysfunction in novel test. Moreover, OP-treated groups exhibited impairments in sociability and social novelty preference in three-chamber social test and social interaction test. In open field test, OP-treated groups increased anxiety-like behavior and change the locomotor activity in mice. Our results first pronounced that exposure to perinatal exposure to OP influences the neuronal development, lead to abnormal behavior in the adult off spring mice.

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Thyroid

AEP857

Association with 3-iodothyronamine improves the effect of levothyroxine on neurocognitive symptoms in a mouse model of adult-onset hypothyroidism

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Adult-onset hypothyroidism is related to anxiety, depression, and impaired neurocognition. Guidelines from all professional societies recommend levothyroxine (LT4) monotherapy as the treatment of choice. However, ~15% hypothyroid patients do not achieve a satisfactory functional level despite TSH within the reference range. The beneficial effects of combining LT4 and liothyronine (LT3) to improve neuropsychiatric functions remains unclear. Recently, 3-iodothyronamine (T1AM), a thyroid hormone derivative, demonstrated pro-learning and anti-amnestic effects *in vivo*. Notably, decreased T1AM tissue levels were found in pharmacological rodent model of hypothyroidism, even after adequate hormonal replacement with LT4. Here, in a mouse model of adult-onset hypothyroidism, we aimed at comparing various combinations of classical and non-classical thyroid hormones on hippocampus-dependent memory, anxiety- and depression-like behaviors. Six-week-old C57BL/6J male mice ($n=41$) were given Methimazole and Potassium Perchlorate (0.20 mg/g/die and 0.30 mg/g/die) in drinking water for 49 days. As controls, $n=8$ littermates received water. At day 21, mice were implanted with subcutaneous ALZET osmotic pumps delivering replacement treatments for 28 days. We had 6 experimental groups, as follows: (1) hypothyroid, $n=9$; (2) LT4, $n=6$; (3) LT4&LT3, $n=9$; (4) LT4&T1AM, $n=8$; (5) T1AM, $n=9$; (6) euthyroid, $n=8$. T4 and T3 serum concentrations were determined, by high performance liquid chromatography coupled with tandem mass spectroscopy (HPLC-MS/MS), and confirmed the validity of our model. Mice were exposed to: (i) Elevated Plus Maze, for the assessment of anxiety-related behaviors; (ii) Open Field Test, for locomotion; (iii) Novel Object Recognition test, for hippocampus-dependent memory; (iii) Tail Suspension Test, for depression-related behaviors. Hypothyroid mice displayed significantly impaired hippocampus-dependent memory as compared to euthyroid mice (discrimination index, DI=–0.00±0.09 vs 0.28±0.08, t=2.43, $P<0.05$). ANOVA detected a global significant difference in DI among the experimental groups (F (5, 43)=4.038, $P<0.01$). In detail, LT4 monotherapy almost fully restored memory (DI=0.23±0.09). A larger improvement was observed upon LT4 & T1AM replacement, while T1AM did not induce any effect per se. Memory remained disrupted under LT4 & L-T3, possibly due to thyrotoxicosis. These findings were influenced neither by locomotor activity nor by anxiety- and depression-related behaviors, which remained unchanged. In conclusion, in our pharmacological mouse model of adult-onset hypothyroidism, LT4 & T1AM combination fared better than LT4 monotherapy in ameliorating hippocampus-dependent memory, which was disrupted in hypothyroid conditions. Future studies are needed to elucidate the molecular pathways involved in the observed effects.

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AEP858

3-iodothyronamine ameliorates ischemia-induced synaptic dysfunction in mouse entorhinal cortex

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Abnormalities in thyroid hormone (TH) availability and/or metabolism have been hypothesized to contribute to Alzheimer's disease (AD) and to be a risk factor for stroke. Recently, 3-iodothyronamine (T1AM), an endogenous amine putatively derived from TH metabolism, gained interest for its ability to modulate the nervous and the vascular systems. In the present work, we studied the effect of T1AM on ischemia-induced synaptic dysfunction in the entorhinal cortex (EC), a brain region crucially involved in learning and memory and early affected during AD. Moreover, we investigated the role of the trace amine-associated receptor 1 (TAAR1) and its signalling in T1AM-mediated neuroprotection. Field excitatory post-synaptic potentials (fEPSPs) were recorded in EC horizontal slices obtained from WT mice (C57bl). Slices were exposed to an oxygen-glucose deprivation (OGD) protocol for 10 min and then recorded for 50 min after reperfusion. Drugs were perfused to slices for 10 min during the application of OGD. A long-lasting synaptic depression was induced by OGD in C57bl slices (mean fEPSP amplitude in the last 10 min of recording was of 77±4% of baseline, $n=13$ slices, 6 mice). However, T1AM (5 µM) perfusion was capable of preventing the long-lasting synaptic depression after OGD (mean fEPSP amplitude 96±4% of baseline, $n=10$ slices, 6 mice). A similar protective effect was achieved by perfusion with RO5166017 (250 nM), a specific agonist of TAAR1(mean fEPSP amplitude 99±6% of baseline, $n=6$ slices, 4 mice), while T1AM protective effect was abolished in the presence of EPPTB (5 nM), a selective TAAR1 antagonist (mean fEPSP amplitude was of 81±4% of baseline, $n=9$ slices, 4 mice). Moreover, T1AM failed to protect against ischemia in the presence of a TRKB IgG capable of blocking BDNF (1 µg/ml) (mean fEPSP amplitude 55±4% of baseline, $n=12$ slices, 4 mice), or in the presence of an antibody against TRKB (1 µg/ml) (mean fEPSP amplitude 63±5% of baseline, $n=7$, 3 mice), or with a selective PI3K inhibitor, LY294002 (10 nM) (mean fEPSP amplitude 58±5%, $n=7$ slices, 3 mice), suggesting that BDNF signalling may contribute T1AM-mediated neuroprotection. Interestingly, the putative T1AM precursor, triiodothyronine (T3), and its oxidative metabolite, the 3-iodothyroacetic acid (TA1), didn't possess the same neuroprotective ability. Therefore, our results demonstrate that T1AM can ameliorate ischemia-induced synaptic dysfunction in the mouse EC and suggest that T1AM neuroprotection is mediated by TAAR1 signalling.

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AEP859

Importance of maternal thyroid hormone for programming the cardiovascular system in the male offspring

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Thyroid hormone (TH) plays an important role for brain development. As the fetal thyroid gland only starts providing hormone at the end of pregnancy, the developing brain crucially depends on maternal thyroid hormone in early developmental periods. In previous studies, we have observed that in particular the central control of cardiovascular functions critically depends on maternal thyroid hormone for proper development; however, the precise window when the hormone is beneficial has remained to be determined. To address this question, we used mice expressing a mutant thyroid hormone receptor α1 (TRα1+m), which exhibits a reduced sensitivity to the hormone. Under physiological conditions, this leads to a receptor-mediated hypothyroid phenotype; however, the receptor can be reactivated during any given time period by raising the circulating thyroid hormone levels pharmacologically. For this study, we mated male TRα1m mice with wildtype females and treated these dams either in the first or the second half of pregnancy with thyroid hormone. We then compared the resulting TRα1+m offspring, in which TRα1 signaling had be reactivated during these developmental windows, with the resulting wildtype mice that were overexposed as embryos to thyroid hormonespecifically in these periods and untreated control offspring of both genders. In our study, we found a significant decrease of heart weight in male TRα1+m independent of the treatment, suggesting that this phenotype is an acute and not a developmental action of the mutant TRα1. Most remarkably, we found a significant increase in heart rate in the wildtype male offspring that were exposed in the second half of the pregnancy to elevated thyroid hormone, underlining our previous findings that this period is absolutely crucial for the establishment of the central control of cardiovascular functions. Taken together our findings demonstrate that maternal thyroid hormone is of particular relevance for establishing the cardiovascular set points during the second half of pregnancy. The data therefore further advocate current initiatives to routinely monitor thyroid hormone levels during pregnancy to avoid adverse health effects in the offspring.

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AEP860

The natural history of benign thyroid nodules: 10 years follow-up

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Background and aim
The incidental detection of asymptomatic thyroid nodules (TNs) has increased over time. Over 90% of newly diagnosed TNs are either cytologically or sonographically benign. This study aimed to determine the frequency and magnitude of changes in TNs size over time.
Methods
We performed a prospective, multicenter, observational study involving consecutive euthyroid patients with 1–4 asymptomatic, sonographically or cytologically benign TNs. The study cohort was recruited between 2006 and 2008. A yearly neck ultrasound was performed. TNs growth, defined as the first occurrence of volume increase during the follow-up, was considered significant if an increase of ≥20% was recorded in at least 2 diameters, with a minimum increase of 2 mm. After 10 years of follow-up, data were analyzed.
Results
992 consecutive patients were enrolled, and 1567 TNs were evaluated. The median follow-up was 8 years (IQR 6.2–10 years). TNs growthoccurred in 356 patients (35.9%; 95% CI, 32.9–38.9). The median time to growth was 2 years (IQR 1–4 years). Stable nodules were reported in 578 patients (58.3%; 95% CI 55.2–61.3), while 58 patients had no growing TNs and/or at least a shrunk nodule (5.8%; 95% CI 4.4–7.3). New TNs ($n=456$) appeared in 205 patients (20.7%; 95% CI 18.1–23.2). 242 (24.4%) patients finished the 10-years follow-up. Among these, the final nodule volume did not show a significant difference compared to baseline. 148 out of 242 patients showed a linear increase in TNs volume, mainly evident after the 3-years follow-up. Baseline factors associated with nodule growth were the same identified during the already published first 5-year analysis (multiple nodules, larger nodule baseline volume, male sex, age <45 years). However, the evidence of growth during the first 2 years follow-up was the strongest predictor of future growth (HR 7.43; 95% CI 5.82–9.48; $P<0.0001$). Growing nodules had a median doubling time of 3 years, while the whole cohort had a median doubling time of 26.6 years.
Conclusions
A small fraction of nodules showed a significant size increase during 10 years of serial evaluation, and it is possible to predict their behavior with early (2 years) follow-up data. These findings allow us to estimate the interval of monitoring and support the view that patients with sonographically or cytologically benign TNs can be safely followed with less frequent examinations.
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AEP861

How will my life with Graves' disease be? Two years of serial, longitudinal follow-up of thyroid-related quality of life in patients with Graves' disease

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Objectives
Quality of life (QoL) is severely affected in Graves' disease (GD) but long-term longitudinal assessment of QoL is lacking. Furthermore, whether QoL is comparable to controls after treatment of GD is unclear. For the first time, we present serial, longitudinal data on thyroid-related QoL during 24 months of follow-up in a cohort of newly diagnosed GD patients. In addition, we compare QoL in GD and controls.
Methods
All patients were treated with anti-thyroid medication according to standard care. QoL was assessed on eight occasions using the highly validated, disease-specific ThyPRO-39 questionnaire (score 0–100, higher worse). Patients were excluded from analysis in case of relapse. A matched euthyroid control group ($n=55$) also completed ThyPRO-39. All patients were enrolled in the DAGMAR study (clinicaltrial.gov NCT02384668) a randomized double-blind trial on effects of vitamin D (70 mg/d) vs placebo on the clinical course of GD. Longitudinal data were analyzed in the entire cohort using linear mixed modeling with time, intervention group (vitamin D or placebo) and their interaction term. Changes in QoL-scores are reported as the main effect of time. A 'large' change has previously been defined as >16 points difference in score. The QoL scores of placebo treated GD and controls (one assessment) were compared using Wilcoxon ranksum test.
Results
Eighty-six hyperthyroid GD-patients (86% females, mean age 41 ± 14) were enrolled. Baseline QoL scores were 50 ± 19 and 47 ± 19 on the Hyperthyroid Symptoms and the Composite QoL Scales. Compared to baseline scores, 'large' improvements were observed at six weeks on Hyperthyroid Symptoms, Tiredness, Impaired Daily Life, Composite QoL and Emotional Susceptibility Scales, whereas Cognitive Complaints showed large improvement at six months. Significant improvements of QoL beyond six months were observed on the Hyperthyroid Symptoms, Tiredness, and Composite QoL Scales. Vitamin D supplementation did not improve QoL. Compared to the controls, the QoL scores among the GD patients remained significantly worse at every assessments for the Hyperthyroid Symptoms, Tiredness and Cognitive Complaints Scales. For the Impaired Daily Life and Emotional Susceptibility Scales, QoL scores remained worse until six months.
Conclusion
These novel data demonstrate that despite marked and early improvement of QoL with anti-thyroid treatment, QoL impairments in GD were prolonged, albeit improved beyond 6 months of treatment. Importantly, compared to controls GD patients have worse mental QoL for as long as 6 or even 24 months after diagnosis, despite being euthyroid and/or in remission.
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AEP862

Influence of care pathway on thyroid nodule surgery relevance

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Objective
Guidelines recommend using fine needle aspiration cytology (FNAC) to guide thyroid nodule surgical indication, however to what extent these guidelines are followed remains unclear. This study aimed to analyze the quality of the preoperative care pathway and the influence of the care pathway on surgical indications relevance.
Design
Nationwide historical cohort study based on data from a sample (1/97th) of French health insurance beneficiaries.
Methods
Evaluation of the care pathway of adult patients operated between 2012 and 2015 during the year preceding thyroid nodule surgery. Pathways containing a FNAC were called 'FNAC' or 'FNAC+ENDO' when including an endocrinology consultation; whereasthe no FNAC pathway was called 'NO FNAC'. The main outcome was the malignant nature of the nodule.
Results
Among the 1080 patients included in the study, 'FNAC+ENDO' was found in 197 (18.2%) patients, 'FNAC'in 207 (19.2%) and 'NO FNAC' in 676 (62.6%).A cancer diagnosis was recorded in 72 (36.5%) 'FNAC+ENDO' patients and 66 (31.9%) 'FNAC' patients, against 119 (17.6%) 'NO FNAC' patients. As compared to 'NO FNAC', 'FNAC+ENDO' care pathway was significantly associated with thyroid cancer diagnosis (OR 2.67; 95% CI 1.88–3.81; *P*-value <0.001) as was'FNAC' (OR 2.09; 95% CI 1.46–2.98; *P*-value <0.001). Surgeries performed in university hospitals were significantly associated with thyroid cancer diagnosis (OR 1.61; 95% CI 1.19–2.17; P-value = 0.002).
Conclusions
Guideline compliancewas insufficient but was associated with more relevant surgical indications. A trend towards improvement in compliance with guidelines was observed over the years.
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AEP863

Retrospective incidence of NIFTP. A large multicentre Iberic study of over 3000 neoplasms

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The newly created NIFTP category (non-invasive follicular thyroid neoplasm with papillary-like nuclear features) has had a notorious impact in the management of thyroid neoplasms. Its incidence appears to be higher in western countries than Asiatic, but there are few studies including more than one institution.
Objectives
To evaluate retrospectively the incidence of NITFP in a multicentre study in two adjacent countries as well as to compare the results among institutions.
Methods
Sixteen institutions from Spain (15) and Portugal (1) took part in the study. Each of them made a retrospective review of its surgical cases of Follicular Variant of Papillary Thyroid Carcinoma (FVPTC) and Well-Differentiated Tumour of Uncertain Malignant Potential (WDT-UMP) from January 1st, 2005 to December 31th, 2015. The final pathology reports were reviewed and potential NIFTPs over 5 mm were retrieved for a pathological review.
Results
Among the 3185 cases with the diagnosis of papillary thyroid carcinoma (PTC) there were 900 (28.3%) of FVPTC added to 14 cases of WDT-UMP. After the review of the archived slides of the selected cases by the own pathologist in each centre, 175 were reclassified as NIFTP, 35 of them (20%) between 5 and 10 mm of size. They included seven of 14 WDT-UMP (50%) and 168 of 900 FVPTC (18.7%). The distribution by centre varied from 0% (no NIFTP among 16 FVPTC) in the centre with the lowest incidence, to 43.5% (10 NIFTP among 23 FVPTC) in the hospital with the highest incidence. The 3 institutions with more than 100 cases of FVPTC revised had an incidence from 15.9 to 25.4%. The most frequent cause of surgery was cytological or histological study with fine needle aspiration or core needle biopsy, including 58.3% of cases. Eight glands showed two foci of NIFTPs and two of them three foci. Mean size of the main focus of NIFTP was 21.8 mm (s.d.: 14.8).
Conclusion
In our geographic area, NIFTPs comprise 5.3% and 18.7% of cases previously classified as PTC and FVPTC respectively. We found that half of neoplasms named as WDT-UMP matched to NIFTP in its histological re-evaluation. The incidence of this diagnosis varies widely between hospitals separated by a few hundred kilometres. The cause of this difference remains elusive, and we propose that it could lie in the stringency of histological criteria for assigning a tumour as PTC when each pathologist evaluates nuclear changes.

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AEP864

Multiple endocrine neoplasia Type 1 (Men1) – genetic variants of Men1 gene in the czech population

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant hereditary tumor syndrome. Common manifestations include more than 20 tumors of the parathyroid, pituitary and pancreatic glands and others non-endocrine tumors. The majority of patients carry a germline mutation in a tumor-suppressor gene *MEN1*, that encodes nuclear protein menin, ubiquitously expressed. So fare, more than 600 germline or somatic mutations have been reported over the entire coding region. Approximately 70% of mutations lead to premature truncation of menin (20% nonsense, 50% frame shift).
Subjects
In years 20015–2019 we have screened 72 basic patients with suspected MEN1 syndrome from the whole Czech republic and in positive findings we have examined their 20 direct relatives.
Methods
All 10 exons with introns flanking regions and 3´and 5´ UTR regions of *MEN1* gene were analyzed by next generation sequencing (NGS) using kit Nextera XT on Miseq (Illumina).
Results
Sexteen germline mutations were identified in 18 of 72 basic patients with suspected MEN1 syndrome and in 12 of their 20 relatives. Six of detected variants have not been described yet: S113Qfs3X, D123Mfs31X, L267R, G281W, c.1049+9G>C and E392Gfs17X. In silico analysis detected these variants as pathogenic or probably pathogenic. Ten variants were previously described in families with MEN1 syndrome or familial primary hyperparathyroidism: I85Sfs32X, I85Lfs32X, T210Sfs13X, S226X, Q258X, c.784–9G>A, N374Tfs3X, D418H, C421R and R516Pfs15X. Furthermore, we have identified 3 intron variants with uncertain significance (by in silico analysis): c.–55C>T (pathogenic moderate), c.913–142C>T (likely benign) and c.913–159G>A (possible effect on splice site). We could not assess their clinical impact.
Conclusion
We confirmed the diagnosis of MEN1 syndrome in 25% of suspected basic patients and in 60% of their direct relatives. 62.5% from detected variants leaded to truncated menin (50% frame shift and 12.5% nonsense mutations), 25% were missense variants and 12.5% of the variants affected splice site. As regards newly detected genetic variants, we continue to examine other members of families to confirm the clinical impact of the variants.
Support
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AEP865

Targeting RAC1 signaling to potentiate the positive effect of MAPK pathway inhibition on radioiodine uptake

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Introduction
The Sodium Iodide Symporter (NIS) is responsible for active transport of iodide into thyroid follicular cells, enabling the use of radioactive iodine (RAI) for treatment of metastatic disease. Still, a significant proportion of patients with advanced forms of thyroid cancer (TC) became refractory to RAI therapy. Defective NIS expression is the main reason for impaired iodide uptake in TC and NIS downregulation has been associated with several pathways linked to malignant transformation. Activation of MAPK pathway has emerged as a key signaling implicated in thyroid tumorigenesis and NIS downregulation has been associated with the overactivation of this pathway. Consistently, several strategies aiming at inhibiting the MAPK-pathway have been developed with the goal of increasing the uptake of iodide in refractory tumors to allow treatment with RAI. Nevertheless, the use of MAPK-pathway inhibitors only partly restored NIS expression in several experimental

models. Thus, therapeutic strategies directed to additional targets implicated in NIS upregulation could provide an additional level of adjuvant therapeutic intervention to enhance RAI uptake and increase clinical effectiveness. We have recently shown that the small GTPase RAC1 has a positive impact on TSH-induced NIS expression and iodide uptake in thyroid cells.
Objective
We evaluated whether the recovery of NIS expression induced by inhibition of the MAPK pathway can be increased by potentiating RAC1 activity in thyroid cell systems.
Methods
NRASQ61R and BRAFV600E mutantswere ectopically expressed in the thyroid follicular cell lines PCCL3 and FRTL5 by lentiviral transduction. The papillary TC-derived BCPAP cell line, in which the MAPK-pathway is constitutively activated by the BRAFV600E mutation, was also used. Cell lines were transfected with GFP-empty vector or GFP-G12V RAC1 expressing constructs, in the presence or absence of the MEK inhibitor AZD-6244. The impact of AZD-6244 treatment and ectopic overexpression of the constitutively active G12V-RAC1 mutant on NIS transcript levels was addressed by RT-qPCR.
Results
Treatment of both PCCL3 and FRTL5 cell lines with AZD-6244 consistently increased NIS transcript levels, overcoming the negative effect on NIS induced by NRAQ61R and BRAFV600E overexpression. Interestingly, inhibition of RAC1 signaling was able to partially block the AZD-6244-mediated positive impact on NIS expression. A relevant increase in NIS levels was also observed following treatment of BCPAP cancer cells with AZD-6244. Notably, this increase was considerably improved by the presence of active RAC1.
Conclusions
Overall, our data support the potential of the stimulation of RAC1 activity in enhancing NIS expression in the thyroid context.

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AEP866

Radioactive Iodine-Refractory (RAI) Differentiated Thyroid Cancer (rDTC): Analysis of the Canadian Patient Support Program (PSP) for the Prescription and Treatment Patterns of Lenvatinib (LEN)

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Differentiated thyroid carcinoma (DTC) is viewed as an indolent disease but 5–15% of patients (pts) become refractory to RAI treatment. This is associated with poor prognosis, a 3–6 years life expectancy and accounts for approximately 200 deaths per year in Canada. There is no universal definition of rDCT and management evolves over time, with either monitoring or systemic therapy including LEN. In the Select Study on LEN in DTC, LEN provided a 19.4 month (mo) median PFS (progression free survival) and an objective response rate of 60.2%; however, all ptsexperienced some toxicity. In Canada, a PSP was created to offer LEN to pts with rDTC prior to public funding. We report the prescription practices and treatment patterns of these pts. Between August 2015 and January 2019, 223 pts with rDTC started LEN as part of the PSP. Prescriber information, patient demographics, start and discontinuation dates, starting/modification doses and reasons for discontinuation were ascertained whenever possible and are described in the statistics. Kaplan-Meyer method was used to estimate persistency on LEN, defined as time from first prescription to discontinuation. Treating physicians were medical oncologists ($n=141$), endocrinologists ($n=21$) or other various disciplines ($n=55$). Two-hundred twenty-three rDTC pts were analyzed (42% female, mean age 63.4 years). Median study follow-up was 15.8 mo. Mean starting dose was 21.2 mg using 24 mg for 158 pts (66%), 20mg for 35 pts (15%) and lower for 47 pts. Median KM estimate of persistency on LEN was 15.8 mo and was similar for pts starting on full or reduced dose. Treatment persistency was similar between all provinces but there was a trend favouring prescribers with more than one patient in the PSP versus those with only one patient (18.0 vs 10.2 mo) and for pts treated by endocrinologists compared to other specialties (10.4 vs 6.0 mo). There was also a trend for longer persistency in pts who had dose modifications compared to pts treated with constant doses (19.0 mo vs 9.8 mo). LEN was discontinued in 112 patients (39 deaths from disease, 23 progressive disease/palliation, 15 for medical reasons other than toxicity [including decision to pursue alternative therapy], 21 undisclosed/other reasons and only 14 from toxicity). To date, this is the largest presented real-world analysis of the treatment patterns of LEN in pts with rDTC and our estimates of treatment duration as proxy for effectiveness are comparable to the phase 3 SELECT trial.

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AEP867

Loss of heterozygosity (LOH) at 12q24.11 as a potential marker of follicular thyroid lesions malignancy

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Introduction
Pre- and postsurgical differentiation between follicular thyroid adenoma (FTA) and follicular thyroid cancer (FTC) represents a significant diagnostic challenge. Typical markers of malignancy may appear as specific genetic alterations. Next-generation sequencing (NGS) studies bring information about single point mutations, however better insight into follicular thyroid lesions genetic landscape, encompassing bigger rearrangements, is needed.
Aim
The study aimed to compare FTA and FTC using the high-resolution single nucleotide polymorphism (SNP) array and identify recurrent regions of LOH (loss of heterozygosity), which may support preoperative differentiation and a better understanding of those entities.
Material and methods
We analyzed formalin-fixed paraffin-embedded (FFPE) samples acquired from 32 patients, Caucasians (median age at diagnosis: 58), diagnosed with follicular thyroid lesions: 16 diagnosed with FTA and 16 diagnosed with FTC. Both groups were adjusted for age and gender. Genomic DNA was isolated from dissected FFPE tissues using *QIAamp DNA FFPE Tissue Kit* (*Roche*). The *OncoScan* array (*Affymetrix*, *Thermo Fisher*) was used to determine structural rearrangements and LOH utilizing the SNP markers. The obtained data from genomic experiments was subjected for analysis using dedicated *OncoScan Console 1.3* and *ChAS v4* software and compared with clinical data.
Results
The most common LOH present in both FTA (63%) and FTC (69%) was 16p12.1p11.1 LOH (7.50 Mb in size) that encompasses *TP53G3* and its several alternative splicing transcripts (*TP53G3B*, *TP53G3C*, *TP53G3D*). The only LOH present exclusively in FTA patients (56% vs 0%) was 11p11.2p11.12 (5.40 Mb), including *KAI1*, a metastasis suppressor gene. Another LOH on chromosome 20 (q11.21-q11.23, 6.89 Mb) predominated also in FTA (31% vs 6%, $P=0.172$). The alteration which tended to be detected more often in FTC (38% vs 6%, $P=0.083$) was 12q24.11q24.13 (3.99 Mb) overlapping *FOXN4*, *MYL2*, *PTPN11*, *RASAL1*genes (with a suspected role in tumor progression). Another two LOH occurred with a similar frequency in both FTC and FTA (56% vs 44%, and 56% vs 31%): 3p21.31p21.1 (6.40 Mb) encompassing *SMARCC1*, *FBXW12*, *PARP3* and 15q15.1q21.1 (3.62 Mb) including *TYRO3*.
Conclusions
The results indicate that FTA and FTC may share a common genetic background, even though differentiating rearrangements may also be detected. 12q24.11q24.13 LOH may constitute a possible marker of malignancy as it includes genes directly associated with thyroid cancer pathogenesis. Genomic screening demonstrates the complexity of follicular thyroid lesions' genetic background and enables the identification of new genetic rearrangements contributing to FTC pathogenesis.

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AEP868

Changes in volume of the thyroid nodule with a previous benign cytological study according to the ultrasound patterns proposed by ATA 2015

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Objective
To understand the factors associated with changes in thyroid nodule volume with previous benign citology.
Material and methods
This is a prospective single-center observational study. We included patients with a benign citology from March/2016 to May/2018 and ultrasound follow-up after 12–24 months. Initially we determined the nodule size (volume in ml), and its risk of malignancy was classified according to ATA 2015 criteria. Volume changes were defined as following: decrease (decrease >20%), stability (between –20% and +20%), non-significant growth (increase between 20% and 50%) or significant growth (increase >50%). We defined the nodule growth rate as the time it takes for a nodule to double its inicial volume (volume doubling time, VDT), measured in months. Statistic analysis was performed with SPSS 20.0.
Results
There were included 200 thyroid nodules (186 patients) with a mean follow-up of 18.2±6.4 months. The mean age was 50.4±13.6 years; 27 (13.5%) were males; initial TSH was 1.6±1.3 mU/l; 54 (27%) had positive autoimmunity and 142 (71%) were multinodular. Mean characteristics of node size: larger diameter 28.8±11.5 mm; volume 8.6 ml (range 0.26–69.8). Risk of malignancy according to ATA criteria: 44 (22%) very low; 119 (59.5%) low; 16 (8%) intermediate; 3 (1.5%) high and 18 (9%) not classifiable. The distribution of the nodules by volume change was: 25 (12.5%) decreased; 94 (47%) remained stable; 53 (26.5%) presented non-significant growth and 28 (14%) showed significant growth.
None of the basal characteristics of the nodules (sex, age, TSH, autoimmunity, nodularity, volume or ATA criteria) was significant in association with significant growth. However, we observed that the very low risk nodules decreased in a greater proportion than the others ($P<0.001$). From among the nodules with any growth, only 14 (10.1%) had a VDT less than 24 months. Six malignant nodules (3.3%) were detected after follow-up. Four (66.6%) did not show significant growth. Their risk of malignancy according to ATA criteria were: 3 (2.5%) low risk; 2 (12.5%) intermediate risk; 1 (33.3%) high risk.
Conclusions
1) a low proportion of thyroid nodules show significant growth after follow-up; 2) none of the variables studied are able to predict the significant growth of the nodules; 3) The ATA criteria have been useful for detecting misdiagnosed malignancy in the initial assessment.

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AEP869

Tocilizumab for corticoid-resistant Graves' orbitopathy: A case report

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Introduction
Graves' ophthalmopathy (GO) is an autoimmune disorder that constitutes a major clinical and therapeutic challenge. Current treatment options for moderate-to-severe GO include immunotherapy, orbital radiotherapy and decompression surgery. Limited drugs of proven efficacy are available for the treatment of people with GO. Given the role in the pathogenesis of GO of interleukin (IL)-6 expression in adipocytes, fibroblasts and macrophages, the proposed theory is that inhibition of IL-6 by tocilizumab may be an effective treatment in GO by directly reducing the inflammatory response. We report a case of severe GO treated with tocilizumab. Efficacy and safety of the therapy is discussed.
Case report
A 48-year-old woman, former smoker and diagnosed with Graves' hyperthyroidism was referred by Ophthalmology Department to Internal Medicine Unit because of corticoid-resistant GO. She had been diagnosed with hyperthyroidism ten years ago and undergone thyroid radio ablation therapy at the onset of her disease, reaching euthyroidism since then. At the time of our evaluation, the patient had no general symptoms of thyroid disease. A biochemical profile including thyroid hormones was also normal. She presented with bilateral eyelid swelling, orbital pain, redness and tearing. Her Clinical Activity Score (CAS) was 5 out of 7. She previously received bolus of methylprednisolone with a weak response. A magnetic resonance imaging orbits scan showed intense gadolinium-enhanced images and enlargement of the extraocular muscles, more prominent of the medial and lateral recti muscles in both orbits. The patient rejected radiotherapy. 'Off-label' authorization for the use of tocilizumab was asked to Pharmacy Commission of our centre. After its approbation, she received tocilizumab 8 mg/kg monthly. Three months later, the patient was well, no side effect was documented and her CAS was 1 out of 7.
Conclusions
This clinical report confirm the relative efficacy and tolerability profile of intravenous tocilizumab in severe or corticosteroid-resistant GO.

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AEP870

Dietary pattern and oxidative stress markers in hashimoto's thyroiditis

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Objective
Oxidative stress has been implicated in the pathogenesis of several immune-mediated disorders, including autoimmune thyroid disease. Aim of our study was to investigate the relationship between dietary habit and redox homeostasis, in relationship with thyroid autoimmunity.
Materials and methods
We enrolled 200 healthy subjects (173 F, mean age 35±12). None of them was under any pharmacological treatment. Exclusion criteria: any infectious/inflammatory/autoimmune comorbidity, kidney failure, diabetes, cancer. In each subject, we measured; serum TSH, free thyroxine andanti-thyroid antibodies; plasma oxidative stress markers (Table 1). A validated questionnaire on dietary habits, evaluating the intake frequencies of food groups (meat, fish, cereals, fruits and vegetables, dairy products) was submitted to each participant.
Results
Among the 200 recruited subjects, 81 (71 F, mean age 38±11 yr) were diagnosed with euthyroid Hashimoto's thyroiditis (HT), the remaining 119 (102 F, mean age 33±12 yr) served as controls. In HT subjects, AGEs, markers of oxidative stress, were significantly higher ($P=0.0001$), and anti-oxidants GPX, TRX and TEAA lower ($P=0.02$, $P=0.02$, $P=0.002$, respectively) than controls, clearly indicating a condition of oxidative stress (Table 1). In questionnaires, HT subjects reported higher intake frequencies of animal foods (meat $P=0.0001$; fish, $P=0.002$; dairy products, $P=0.030$) compared to controls, that, in turn, reported higher intake frequencies of plant foods (legumes, $P=0.010$; fruits and vegetables, $P=0.030$). Stepwise regression models demonstrated a significant dependence of oxidative stress parameters from consumption of animal foods: meat dietary intake was associated with low levels of GPX ($P=0.048$) and TRX ($P=0.007$), and dairy products intake was associated to low levels of TEAA ($P=0.020$).
Conclusions
The present study provides further evidence that oxidative stress increases in euthyroid HT. Moreover, it suggests a positive influence of low intakes of animalfoods on the oxidative/antioxidative balance, and a potential protective effect of such dietary habit towards oxidative stress-related disorders.

Table 1

	OXIDATIVE STRESS MARKERS § (mean ± SD)						
	AGEs	AOPP	SOD	GPX	TRX	GR	TEAA
	AU/g prot	µmol EqCIT/L	U/ml	U/ml	U/ml	U/ml	mM TE
HT (n=81)	165.85 (±70.09)	1.1335 (±0.35)	4.8189 (±0.71)	0.6100 (±0.12)	1.7202 (±0.73)	65.426 (±20.27)	1.5322 (±0.25)
Controls (n= 119)	114.51 (±55.97)	1.0554 (±0.34)	5.0598 (±1.05)	0.6531 (±0.12)	2.0809 (±0.90)	71.525 (±20.34)	1.5676 (±0.10)
P*	0.0001	0.162	0.121	0.020	0.023	0.282	0.002

§AGEs: Advanced glycation End Products; AOPPs: Advanced Oxidation Protein Products; SOD: Superoxide dismutase; GPX: Glutathione Peroxidase; TRX: Thioredoxin; GR: Glutathione reductase; TEAA, Trolox-Equivalent Anti-oxidant Activity.
* In order to assess any significant differences between HT cases and controls, the Mann–Whitney U-test was applied for all examined numerical parameters. A p-value of<0.050 was considered to be statistically significant. In bolt significant P values.

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AEP871

Catch it if you know – A rare case of impaired TSH measurement

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Introduction
Thyreotropin (TSH) is a glycoprotein containing an alpha-subunit similar to other glycoproteins (LH, FSH, ACTH, HCG) and a unique beta-subunit which reacts with the alpha-subunit in binding to the TSH-receptor. Low TSH levels are usually evidence of primary hyperthyreoidism as in Graves diseases/ toxic goiter or thyroiditis, or a result of secondary hypothyroidism in case of diseases of the pituitary gland. This case shows a rare variant causing apparently low TSH levels in a euthyroid patient due to altered immunoreactivity with the serum TSH measurement.
Case presentation
A 37-year old patient was referred to our clinic with subclinical hyperthyroidism and a discrepancy in TSH results from his general practitioner (Abbott assay at a contract). Clinically, there were no signs of hyperthyroidism. In the initial laboratory work-up he showed repeatedly low TSH (Siemens assay), negative Anti-TPO and TRAb. After excluding all primary and secondary causes we had the serum sample analyzed for TSH (Roche assay) in a third laboratory, using a different assay, resulting in slightly elevated levels. The following genetic test revealed a homozygous variant in the TSH-beta-subunit, 223A>G (*P*.Arg75Gly), leading to a reduced immunoreactivity with our TSH assay (Siemens Dimension Vista 1500 assay). This mutation was previously described to interfere with other detection assays. With worldwide only 5 cases of homozygous carriers and none in Europe, this sequence variant is very rare, according to genome databases.
Conclusion
This report shows a case of spuriously low TSH measurement in a euthyroid patient. An arginine to glycine substitution at amino acid position 75 in the TSH-beta-subunit reduced immunoreactivity ofthe Siemens Dimension Vista 1500 assay. Generally, state-of-the-art antibody based protein quantification assays offer high sensitivity and specificity; however, missense mutations (even if physiologically irrelevant) may result in falsely low values due to impeded antibody binding. Even if rare, it is important to question conflicting results, especially if they are not in agreement with the clinical findings, as otherwise they can lead to a false diagnosis and mistreatment of patients.

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AEP872

***In vitro* analysis of the effects of Thyroid Hormones on the electrophysiological activity of human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs)**

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Thyroid hormones (TH)shave as a major target the heart, where they regulate many different functions, including the modulation of the heart rate and myocyte contractility. Their effects on ventricular repolarization are controversial and QT prolongation was reported both in patients with hypothyroidism and hyperthyroidism, in their overt or subclinical forms. We analyzed the effects of 3.3′,5.5′-tetraiodo-L-Thyronine (T4), 3.3′,5-triiodo-L-Thyronine (T3) and of 3.3′,5′-triiodo-L-thyronine -reverse T3 (rT3) on Field Potential Duration (FPD), the *in vitro* analog of QT interval, and on induction of arrhythmiausing a human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) cell line, namely the human iCell Cardiomyocytes (Cellular Dynamics International, Inc. Madison, WI, USA, clone 01434)and the very sensitive Maestro Pro Multielectrode Array (MEA) platform (Axion Biosystem, Atlanta, GA, USA). Treatment with T3, at slightly supraphysiological doses (1 nM), induces a significant prolongation of the FPD while, at highly supraphysiological doses (up to 100 nM), T3 is able to induce arrhythmia in our cell system. The maximum effect on FPD was a 25% increase of the FPD, corrected by Fridericia (fFPDc), observed with T3 at the dose of 1 nM, while the major effect on induction of arrythmia was observed with the dose of 100 nM. T3 induces a clear dose-dependent prolongation effect on FPD and is responsible for a dose-dependent induction of arrhythmia. Both effectsare visible long time after exposure of cells to T3, up to 24 hours for the effect on FPD and up to 4 days for those on induction of arrhythmia, suggesting that both effects are mediated by genomic actions. To test this hypothesis, FPD prolongation and induction of arrhythmia were evaluated after preincubation with rT3, the specific antagonist of T3 at the thyroid hormone receptor (TR). Preincubation with rT3 significantly reduced both effects, indicating that interaction with TR is necessary for T3-induced FPD prolongation and arrhythmia. In conclusion, we demonstrated the direct impact of THs treatment on hiPSC-CMselectrophysiology and, in particular, on FPD duration and on the induction of arrhythmia. The present study gives useful insight on the mechanism of T3-induced arrhythmias and open the way to identify new potential diagnostic biomarkers and to develop specific targeted therapies.

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AEP873

Treating thyroid nodules by radiofrequency: The delivered energy should be correlated with the volume reduction rate

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Context
Radiofrequency ablation (RFA) was proven as effective in reducing thyroid nodules' volume. However, whether technical procedure aspects could influence the volume reduction rate (VRR) has not been clarified.
Objective
To analyze the correlation of RFA power, duration and energy with VRR.
Design
Prospective study from June 2018 to December 2019.
Setting
Two primary-care centers using the same RFA procedure.
Patients or other participants
Adult outpatients undergoing a single-session RFA and 1-year post-treatment follow-up.
Intervention
RFA was performed by *moving-shot* technique with internally cooled 18-gauge electrode having a 10-mm active tip. Main outcome measures The VRR was calculated. Technical parameters were the following: median power (P_{median}), effective time of treatment (T_{eff}), energy calculated as $P_{median} \times T_{eff}$ (E_{calc}), and energy delivered per ml as Kcal × 4184 × nodule's volume (E_{del}). Continuous variables were analyzed by the Mann Whitney test. The correlation of the above parameters with VRR was analyzed by linear regression.
Results
Forty-one nodules were included and their VRR 66.6%. RFA was performed with a P_{median} of 55 watts, T_{eff} 10.24 min, E_{calc} 31380 Joules, E_{del} 1473 Joules/mL. E_{del} was significantly correlated with VRR ($P=0.014$) while P_{median}, T_{eff} and E_{calc} not. A strong correlation of E_{del} with VRR was found in nodules <10 ml ($P=0.001$) while no significant correlation was observed in nodules >10 ml.
Conclusions
This study showed that the energy delivered with RFA is the only technical parameter significantly correlated with the VRR of thyroid nodules.

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AEP874

Changes in morphology and gene expressions of neonatally X-irradiated thyroid gland in rats

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Purpose
Exposure to ionizing radiation in childhood has been recognized as a risk factor for the development of thyroid cancer and possibly for other thyroid disorders. However, the effects of neonatal radiation exposure on thyroid

functions have never been explored experimentally despite its potential importance. We have demonstrated that neonatal rat thyroid was sensitive to ionizing radiation, developing specific morphological changes characterized by smaller thyroid follicles. In the present study, we examined the effects on the gene expression potentially related to thyroid carcinogenesis in this model.
Materials and methods
One-week-old male Wistar rats were exposed to cervical X-irradiation at 6 and 12 Gy. For comparison, 8-week-old (adult) rats were cervically X-irradiated at the same doses. Apoptosis in the thyroid follicles was evaluated by the TUNEL staining. Expressions of the gene, including Mct8, Lat4, Braf1, Oct3, CD44, and Abcg2, were measured in the thyroid by the quantitative RT-PCR method.
Results
In rats that received cervical X-irradiation at 1 week old, the colloid size of thyroid follicles decreased at 8 weeks old and afterward. The number of apoptotic cells in the thyroid follicles was increased corresponding to the reduction in follicular size. Significant increases in Braf1, CD44, and Abcg2 mRNAs were noted in neonatally irradiated thyroid at 8 weeks old, while CD44 and Abcg2 expressions were still high at 16 weeks old.
Conclusion
Our results demonstrated that neonatal rat thyroid was sensitive to ionizing radiation, developing specific morphological changes that may be caused by the increase in apoptosis. Persistent elevation of CD44 and Abcg2 expressions in the thyroid after neonatal irradiation may play a role in thyroid cancer development in childhood.

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AEP875

Treatment of hyperthyroidism reduces the systemic oxidative stress load, as measured by biomarkers of RNA and DNA damages

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Background
Increased oxidative stress has been linked to both hypo- and hyperthyroidism. Whole-body oxidative stress can be estimated by the oxidized guanine nucleosides, 8-oxo-7.8-dihydroguanosine (8-oxoGuo) and 8-oxo-7.8-dihydro-2'-deoxyguanosine (8-oxodG), derived from RNA and DNA, respectively. These biomarkers have been associated with increased morbidity and mortality in several diseases but are not well explored in humans with thyroid disorders.
Methods
We measured urinary excretion of 8-oxoGuo and 8-oxodG in 51 hyperthyroid patients (toxic nodular goiter (TNG), $n=30$; Graves' disease (GD), $n=21$) before, or shortly after, initiation of therapy and when stable euthyroidism had been achieved for at least 12 months. Patients with TNG were older (mean: 59 ± 12 s.d. years) than those with GD (50 ± 8 years). Mean follow-up time was 17.2 ± 4.6 and 22.9 ± 8.9 months for TNG and GD, respectively. All patients with TNG were treated with radioiodine, except for one who underwent thyroidectomy. GD patients were treated with methimazole andtwo of whom also received radioiodine.
Results
Both oxidative stress markers correlated positively with age (8-oxoGuo: $P<0.001$; 8-oxodG: $P=0.003$). After adjustment, the baseline urinary excretions correlated with the severity of the disease, reflected by the plasma levels ofthyroxine (8-oxoGuo: $P=0.002$; 8-oxodG: $P=0.021$), and were significantly higher in GD than in TNG ($P=0.001$ for both biomarkers). Treatment significantly affected the excretions of the oxidative stress markers. In TNG, 8-oxoGuo decreased from geometric mean (GM) 2.11 nmol/mmol (95% CI : 1.85–2.39) to 1.91 nmol/mmol (95% CI : 1.67–2.19), $P=0.001$, while 8-oxodG decreased from 1.65 nmol/mmol (95% CI : 1.41–1.93) to 1.48 nmol/mmol (95% CI : 1.27–1.74), $P=0.026$. In GD, 8-oxoGuo decreased from 2.25 nmol/mmol (95% CI : 1.95–2.59) to 1.79 nmol/mmol (95% CI : 1.63–1.97), $P=0.0003$, while 8-oxodG decreased from 2.02 nmol/mmol (95% CI : 1.73–2.38) to 1.54 nmol/mmol (95% CI : 1.63–1.97), $P=0.001$. When euthyroid, no between-group differences were found.
Conclusion
Treatment of hyperthyroidism significantly decreased the systemic oxidative stress load by 10–25%, as measured by the urinary excretion of nucleic acid metabolites. The higher values in patients with GD could be due to the more severe hyperthyroidism seen in this condition. Our findings may signify a key factor, explaining the higher morbidity and mortality linked to patients with hyperthyroid diseases, as shown in observational studies.

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AEP876

Diffuse Large B-cell Lymphoma of thyroid gland in an Adolescent girl with Hashimoto's thyroiditis

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Background
Cancer of thyroid gland is rare in childhood, representing 1% of all pediatric malignancies. Primary thyroid lymphoma (PTL) is even rarer accounting for 5% of thyroid malignancies and 2% of extranodal lymphomas. The disease affects mainly adults in thesixth orseventh decade of life, with a female predominance. Most thyroid lymphomas are non-Hodgkin's lymphomas (nHL) of B-cell origin. The most common type is Diffuse Large B- cell Lymphoma (DLBCL). Patients with Hashimoto's thyroiditis (HT) are at greater risk for developing PTL.
Objectives and methods
We describe the case of DLBCL of thyroid in an adolescent girl with a history of HT. To our best of our knowledge, DLBCL in a young child has not been reported in the medical literature.
Results
A 12 -years- old girl with known HT for the last 9 years admitted to our department with a right sided painless progressive swelling of the neck. The physical and ultrasound examination revealed an enlarged thyroid gland and right lymphadenopathy. Full blood count, renal, liver and thyroid function tests were normal while anti-thyroglobulin and thyroid peroxidase antibodies were positive. She has been receiving treatment with levothyroxine since the age of 3. Two FNAs were performed showing suspected lymphoblastic lesions for nHL without precise diagnosis. A neck CT scan revealed a nodular alteration max diameter $2.95 \times 3.9 \times 5.2$ cm of the right thyroid gland and multiple lymph nodes in the neck highly suspicious of the above diagnosis. PET/CT scan confirmed these findings with SUV max = 16.5 and 2.5 in the right thyroid gland and lymph nodes respectively. Ultra-sound guided core needle biopsy was finally performed confirming the diagnosis of DLBCL. CSF analysis showed no tumor cells and the bone marrow aspiration was negative. She was treated according to LMB 2000 – group B protocol with one course COP, two courses COPADM and two courses CYM chemotherapy with no surgical removal of thyroid. The patient had a good response to the treatment with a rapid decrease in the size of the thyroid mass. She is well in herself 8 months post initial diagnosis.
Conclusion
PTLis a rare cause of thyroid malignancy and extranodal lymphomas. However, it should be considered at differential diagnosis of a thyroid mass in patients presenting with a rapidly enlarging neck mass and a history of HT. It is a treatable condition with an excellent prognosis even with the aggressive histological subtypes with no need of thyroidectomy.

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AEP877

Breast cancer metastasis to the thyroid gland – A case report

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Introduction
Metastases to the thyroid are rare (1.4–3% of malignant solid tumors). When present, metastatic cancers mimic the ultrasound image of the thyroid parenchyma, hindering diagnosis. Breast cancer rarely metastasizes to the thyroid.
Case
A 61-year-old woman was referred for goiterin the context of post-surgery evaluation for breast cancer. Thyrotropin (1.14 mIU/l), calcitonin (0.5 pg/ml) and parathyroidhormone (54 pg/ml) levels were normal. Thyroid ultrasound (US) showed a multinodular goiter with maximum nodule size of 4.2 cm at the left thyroid lobe (isoechoic with cystic degeneration areas, with few coarse calcifications and poor peripheral vascularization), scattered smaller hypoechoic nodules up to 4 mm in both lobes and few colloid cystsup to 7 mm, without abnormal lymph nodes. An US-guided FNA was performed at the largest left thyroid lobe nodule, showing benign nodular hyperplasia (Bethesda II). The patient was monitored by US and thyroid hormone testing. Elevated tumormarkers (Ca15–3) led to 18-FDG PET-CT scanning, following oncology consultation. Abnormal uptake (SUV max: 3.7) was noted in the area corresponding to the largest noduleat the left thyroid lobe. Total thyroidectomy was recommended (1.5 years after initial FNA). Histopathological examination revealed the presence of neoplastic infiltration in off-white areas of the right lower lobe of solid carcinoma with morphological and immunophenotypic characteristics compatible with breast tissue origin [CK8–18(+), CK19(+), GATA-3(+), ER(+ >80%), PGR(–), TTF-1(–), Thyroglobulin(–), p40(–), HBME-1(–), Galectin-3(–), S-100(–), Calcitonin(-), Ki67~30%].
Conclusion
In this patient, although FNA had been performed in the larger nodule that had the most suspicious featuresfor possible malignancy, it was considered that the increase in tumor markers and concomitant abnormal uptake in 18-FDG PET-CT increased the likelihood of cancer metastasis. However, histopathology after thyroidectomy revealed breast tissue metastasis in off-white areas at the right lower lobe where ultrasound had noted small hypoechoic nodules and colloid cysts. Although thyroid metastases are not very common, caution should be given especially when thyroid parenchyma lesions coexist with a recent history of malignancy.

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AEP878

Clinical case of autoimmune encephalopathy (Hashimoto) with a psycho-organic syndrome on the background of autoimmune thyroiditis

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Introduction
Hashimoto's Encephalopathy (HE) is an autoimmune inflammatory disease of the brain associated with the production of antithyroid antibodies.
Objective
A clinical case of treatment of severe autoimmune encephalopathy in combination with autoimmune thyroiditis and thyrotoxicosis is presented.
Results
A 59-year-old woman was transferred to the intensive care unit diagnosed with thyrotoxic crisis. Objectively: serious condition, inhibited, disoriented to personality, time and place, inadequate, productive contact is difficult, psychomotor agitation. Asymmetry of the nasolabial triangle. Swallowing is not impaired, movements in the limbs within normal. Normothermy. Heart rate 102 per minute, blood pressure 150/95 mmHg. From the anamnesis, about 5 years of thyrotoxicosis, takes thyreostatics, 3 years ago a similar episode of psycho-productive symptoms occurred, the patient was diagnosed with: 'Pseudodementia Syndrome'; mental status returned to normal without treatment. MRI of the brain: without pathology; in cerebrospinal fluid: protein 3.5 g/l, cytosis 2/3. In the blood and cerebrospinal fluid there is no DNA of herpes simplex virus, cytomegalovirus, Epstein-Barr virus. Procalcitonin and C-reactive protein are normal. Leukocytosis 10.7×10^9/l, urea 10.3 mmol/l, sodium 150 mmol/l, FT4 26.6, TSH 0.07, antibodies to TPO more than 1000. The conclusion of the council of doctors – autoimmune encephalopathy is possible, course of therapeutic plasmapheresis (No. 3) was prescribed in combination with pulse therapy with methylprednisolone (No. 5 of 1000 mg), followed by oral administration, a gradual dose reduction until complete cancellation. By the 7th day, the patient's state with pronounced positive dynamics, in consciousness, adequate, oriented to personality, time and place, some emotional lability and partial amnesia. By laboratory methods- transient hyperglycemia and protein-cell dissociation in cerebrospinal fluid. After 3 months, upon reaching the euthyroid state while taking thyreostatics, the patient underwent total thyroidectomy – without complications. Over the next 2 years, episodes of delirium and severe cognitive impairment were not observed.
Conclusion
It is necessary to consider each case of pronounced cognitive impairment with stroke-like symptoms in the prism of Hashimoto's encephalopathy, which requires timely and special treatment.

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AEP879

Influence of Sodium Iodide symporter expression level on recurrence rate in differentiated thyroid cancer

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The ability of thyroid cell to accumulate iodine is due to presence of sodium iodide symporter (NIS). Differentiated thyroid cancer (DTC) maintain ability to express NIS and thus it makes possible to perform RAI treatment. In case of DTC cells loss the ability of NIS protein production and cell membrane embedding that leads to RAI treatment fail.
The aim of our study was to find a relationship between the level of preoperatively defined NIS and recurrences-free survival after RAI in DTC patients.
Materials and methods
Our study included 205 patients with highly differentiated thyroid cancer. In all patients the level of NIS expression was detected by flow fluorocytometry method in a fine-needle biopsy material. The criteria for inclusion in the study were RAI therapy in the postoperative period, the ability to follow up the patient in the postoperative period up to 60 months. All patients were operated.
Results
RAI therapy was performed in 130 patientsin the postoperative period. Recurrence was detected in 50 patientsin the follow-up period of 60 months. Total thyroidectomy (TT) with central lymph node dissection (CLD) was performed in 72.5% (58/80) of cases in the group without recurrence, compared with the group of patients with detected recurrence, where this operation was performed only in 24% (12/50) of cases. Lateral neck compartment cervical lymph node dissection was performed in 40% of patients in the group with developed recurrence of the disease and in 17.5% of patients without recurrence of the disease. The liner discriminant analysis (LDA) revealed the level of NIS expression less than 1% significantly correlate with the risk of recurrence ($P=0.000037$). In the group of patients with recurrence, the level of NIS expression less than 1% was detected in 31 patients (62%), while in the group without recurrence only in 17 (21.2%).Thus, the recurrence-free survival after RAI is significantly lower in patients with NIS expression less than 1% in primary tumor compared to patients with NIS expression level more than 1%. TT with CLD was performed in all patients with low NIS expression in the group without disease recurrence and decrease in the number of recurrences is possibly associated with the volume of surgical treatment.
Conclusions
The level of NIS expression can be used as a prognostic marker of disease recurrence, particular after RAI. The level of NIS expression less than 1% in the primary tumor is suspicious of RAI-refractory DTC.

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AEP880

Clinical practice survey on BRAF V600E role in the therapeutic decision in indeterminate thyroid cytology

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Introduction
The use of multigene panels in thyroid nodule diagnosis is still limited, due to high costs and need for *ad hoc* sampling. Since *BRAF-V600E* is the commonest genetic alteration in differentiated thyroid cancer, this is the mostly tested genetic parameter in clinical practice.
Aim
To evaluate the use of *BRAF* mutation analysis in wash-out liquid from fine needle aspiration (FNA) in clinical practice, characterizing the cases in which it is requested, and the consequences of genetic test result on therapeutic decisions.
Methods
We considered all the subjects tested for *BRAF-V600E* among those attending the Endocrinology Unit of Modena for FNA between January 2014 and November 2018. After written informed consent, washing fluid was collected together with cytological sample and stored at –20°C. If the clinician deemed it necessary, the sample was thawed, DNA was extracted and genetic test was performed by the high-resolution melting protocol previously described[1]. We collected cytology of nodules according to the 2010 *SIAPEC-IAP* Italian Consensus, and when surgical treatment was performed, histology.
Results
Out of a total of 7112 subjects submitted to FNA, *BRAF* analysis was requested for 681 (9.6%), for a total of 898 nodules: 97% of nodules were indeterminate at cytology, mainly TIR3A (low risk); 2% suspicious or diagnostic for cancer, and genetic test was requested to estimate prognosis; 1% were suspect nodules at ultrasonography with unsuspicious cytology. Only 22 nodules were mutant (*BRAF*+).Most of them were already high risk or suspicious lesions at cytology (64%). One third were TIR3A. Considering the prevalence of *BRAF* mutation among cytological classes of the whole group, only 1% of TIR3A were *BRAF*+. Twenty *BRAF*+ patients were addressed to surgery (one lost at follow-up, one refused): 5% underwent hemithyroidectomy, 25% total thyroidectomy and 70% total thyroidectomy plus central lymph nodes dissection. They all had papillary thyroid cancer. Since 64% of *BRAF*+ were TIR3B-4-5 at cytology, they had surgical indication even before the genetic test. Among the 14 subjects treated with central neck dissection, only 2 had suspect metastasis before surgery; among those who would have had no indication, one third had metastases (only 1 among TIR3A and 2 among TIR3B).
Conclusions
Despite the development of panels, single gene tests are still requested, mainly for nodules with indeterminate low risk cytology. *BRAF* mutation in TIR3A is rare and leads clinicians to more invasive surgery, with questionable clinical utility.
Reference
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AEP881

The diagnostic value of basal and calcium-stimulated procalcitonin for the diagnosis of medullary thyroid cancer: Preliminary results from a multicentric experience

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Background
Calcitonin (CT) is the most sensitive marker for MTC diagnosis. By the way, many pre-analytical, analytical and post-analytical pitfalls worsen its accuracy. Procalcitonin (proCT), a CT precursor, has been suggested as a valuable complementary test in MTC diagnosis, given its stability and the reproducibility between different assay kits.
Material and methods
basal CT (bCT) and proCT (bproCT) and stimulated CT (bCT) and proCT (sproCT) (2–5–10 and 20 minutes)were measured in 37 patients (14M, 23F; median age: 55 years, range: 5–77 years) that underwent surgical excision. At the histological report, 22 were MTC, while the others were C-cell hyperplasias (HCCs) or non-C-cell lesions. 17/37 (45.9%) were carriers of a *RET* mutation. Calcium gluconate at the dose of 25 mg/Kg based on adjusted body weight was administered. bproCT was considered positive when ≥0.04 mg/l, while CT when ≥10 ng/l.
Results
there was a correlation between bCT and bproCT ($P<0.0001$, $r=0.75$). A significant correlation was found between MTC tumor size and bproCT ($P=0.0062$, $r=0.58$), as well as with bCT ($P=0.01$, $r=0.54$).Positive bproCT showed higher specificity than positive bCT in the diagnosis of MTC with respect to non MTC lesions (CCHs or other lesions) (53% vs 40%), with higher positive predictive value (PPV) (70% vs 66.6%). The combination of elevated bCT and bproCT increased the specificity of bCT value from 40% to 67% and its PPV from 67% to 75%. bCT and bproCT showed the same accuracy in *RET*-wild-type (*RET*wt) and *RET*-mutated patients. Applying ROC curve, we could identify a cut-off of 0.07 mg/l for bproCT, able to identify a MTC (sensitivity=68%, specificity=87%, AUC=0.764, $P=0.0009$), regardless of the gender. There was a correlation between sCT and sproCT ($P<0.0001$, $r=0.64$). A positive correlation existed between MTC tumor size and sproCT ($P=0.0018$, $r=0.64$) and with sCT ($P=0.0001$, $r=0.75$). Higher values of median proCT increase were found in MTC versus non-MTC (median increase of 0.22 mg/l in MTC versus 0.02 mg/l in non-MTC, $P=0.0003$). Applying the ROC curve, a sproCT value>0.19 was able to identify an MTC (sensitivity=72%, specificity=93%, AUC: 0.806, $P<0.001$), regardless of the gender. Combining bproCT and sproCT specificity for MTC increased up to 93% (94% VPP).
Conclusions
proCT calcium-stimulated levels are significantly higher in MTC than in non-MTC and are correlate with tumour size. Basal and stimulated proCT can be used in combination with bCT and sCT to increase its specificity in biochemical diagnosis of MTC.
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AEP882

***In vitro* modeling of thyroid cancer cells and fibroblasts interplay**

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Thyroid cancer (TC) is the most common endocrine tumor and its incidence has increased faster than in any other malignancy. Although TCs are usually well differentiated, disease recurrence or persistence is high, because of local and distant metastasis and therapeutic resistance. Among the different genetic alterations, BRAFV600E is the most frequent one. Several studies tried to establish a correlation between BRAFV600E and patients outcome, with controversial results. Nevertheless, the activation of different BRAF downstream pathways influences immune response, matrix remodeling and intra- and extra-cellular pH. All these alterations substantially modify tumor microenvironment and may enhance the survival of cancer-initiating cells and promote therapy resistance. The aim of the study is to investigate the role of BRAF in cancer-associated fibroblast matrix deposition and remodeling in *in vitro* 2D and 3D systems obtained from immortalized and patients-derived cells. In particular, the use of conditioned media and co-cultures of TC cells with different genetic background and fibroblasts is used to generate different extracellular matrices (ECM). The ECM themselves and their effects on cell growth and survival is then analyzed by different techniques, such as western blot, immunofluorescence, real-time PCR, colony assay, sphere formation assays and proliferation assays. Our results show that TC cells with BRAFV600E mutation can significantly increase the proliferation and activation of fibroblasts in respect with BRAF WT TC cells and normal thyrocytes; fibroblasts that have been conditioned with BRAFV600E TC cells can produce an ECM that is thicker and has a different fiber pattern than the one produced from fibroblasts conditioned with BRAF WT TC cells and normal thyrocytes. Moreover, the different matrices differentially influence the survival of BRAF mutated and WT TC cells. As second step, we are currently evaluating the effects of different drugs that acts against BRAF downstream effectors involved in matrix remodeling and metabolism alterations. In conclusion, our *in vitro* model can partially recapitulate the complex environment of human tumors and can be a useful tool for the screening of different anticancer drugs.
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AEP883

Description of thyroid alterations in oncological patients treated with immune checkpoint inhibitors: Experience of a tertiary hospital

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Introduction
There has been an increase in the use of new drugs called immune checkpoint inhibitors (ICPI) used in advanced tumors. Clinical trials have also reported an increased risk of developing immune-related adverse events (IRAEs). Endocrine IRAEs may be particularly relevant.
Material and methods
This is a retrospective study. Patients treated with ICPI were obtained from Medical Oncology departament of the General University Hospital of Albacete from January 2016 to January 2019. We studied demographic and data related to the tumor, ICPI used, the appearance of thyroid function changes during treatment with the drug, as well as number of cycles received and time elapsed until endocrinopathy. The objective of our study was to analyze the appearance of endocrinopathies and the time that elapses until their appearance.
Results
Our sample size was 107 patients: 75 were treated with nivolumab, 19 with pembrolizumab, 8 with atezolizumab and 5 with ipilimumab. 31% were women and 69% men. The average age at diagnosis was 60 years old. The most frequent location of the primary tumor was the lung. Alteration of thyroid function was observed in 24 patients (22%) treated with ICPI. The most frequent thyroid disorder was subclinical hypothyroidism in 11 cases (46%), followed by primary hypothyroidism in 7 patients (29%) and, finally, silent thyroiditis in 6 of them (25%). The average number of cycles received until developing endocrinopathy was 6 and the time elapsed 12.4 weeks.
Conclusions
Thyroid disorders are usual in cancer patients treated with ICPI. The most frequent thyroid disorder is subclinical hypothyroidism. It is advisable to monitor thyroid function in patients treated with these drugs.

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AEP884

Multiple thyroid gland ectopia in a patient with hypopituitarism

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Introduction
Ectopic thyroid tissue is a rare developmental abnormality resulting from aberrant embryogenesis of the thyroid gland during its passage from the floor of the primitive foregut to its final pre-tracheal position. It may be the only functional thyroid tissue or may co-exist with normally located thyroid. Most of the cases are asymptomatic but symptoms related to location, size or function may occur. Possible malignancy potential has also been discussed.
Case report
The patient is a 52-year old women with nanism who was admitted to endocrinology department in November 2014. According to her past medical record at the age of 12 she was diagnosed with hypopituitarism (GH deficiency and hypogonadism) and hypothyroidism due to growth retardation, lack of pubertal development and marked delay in bone maturation. Treatment with Sotropin H and thyroidea siccata was started and continued until the age of 18 when final height of 130 cm was achieved. She had also been found to have microspherocytic hemolytic anemia and right renal hypoplasia since early childhood. On admission to our department she was in a good physical condition, family history was unremarkable but mild intellectual disability was observed. Laboratory tests found clinical hypothyroidism with TSH level of 17.8 mIU/l (0.34–5.60), FT4 was 9.7 pmol/l (7.86–14.40) without thyroid autoantibodies. The ultrasonography of the neck showed no thyroid tissue in the front pretracheal area. Two round-shaped soft tissue masses in the right and left submandibular area were seen. Subsequent technetium 99^{m} pertechnetate scan revealed three foci of tracer concentration in the left submandibular area with no activity at the usual site of the thyroid gland. A MRI of the head and neck showed multiple thyroid ectopy – below the hard palate, at the base of the tongue and just below the hyoid bone. Thyroid functional tests performed two weeks afterwards showed significant elevation of TSH up to 31.95 mIU/l and levothyroxine treatment was initiated.
Conclusion
Review of literature reveals only few cases of multiple thyroid ectopia reported so far. Although the molecular mechanisms involved in thyroid dysgenesis are not fully known, studies have shown that mutations in regulatory genes expressed in the developing thyroid could be responsible for the abnormal thyroid migration as well as congenital abnormalities in other organs as seen in our patient.

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AEP885

Clinical severity score (CSS) and graves' recurrent events after therapy (GREAT) score could predict radioiodine efficacy for treatment of Graves' disease relapse

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Background
Antithyroid drugs (ATDs) are the first line treatment for Graves' disease in Europe and Asia. However, their long term-efficacy is doubtful, with a high disease relapse rate after discontinuation. Radioiodine and surgery can be used as a second line therapy as definitive approaches after ATDs failure. In recent years, the GREAT and the CSS scores have been suggested to assess the risk of relapse at the time of disease onset, but no data are available about their ability to predict radioiodine treatment efficacy
Objective
To assess whether the GREAT and the CSS scores are able to predict radioiodine therapy efficacy.
Materials and methods
Our retrospective observational cohort study was conducted on 162 patients affected by Graves' disease relapse and treated with radioactive iodine from 2005 to 2013. GREAT and CSS scores were performed for all subjects, who were stratified according to the three defined classes (1 mild, 2 moderate, 3 severe). The failure of radioiodine treatment was assessed as persistence of hyperthyroidism after more than 6 months from radioiodine in the absence of L-thyroxine treatment. Chi-Square and Cox Regression Analysis were used to compare GREAT and CSS classes with treatment efficacy.
Results
Mean dose of radioiodine administered was 11.96 mCi. In 138 (86.3%) patients, radioactive iodine was effective in inducing hypothyroidism or euthyroidism. The GREAT and the CSS scores were positively correlated to each other ($P=0.001$; R2 0.445). No response to radioiodine treatment was found in 12/52 and 4/15 patients with CSS and GREAT scores class 3 respectively. In univariate regression analysis, the lack of efficacy of radioiodine therapy was positively correlated with higher thyrotropin-related antibodies (TRAb) title ($P=0.030$), higher CSS class ($P=0.011$), higher GREAT class ($P=0.039$) and larger thyroid volume ($P=0.004$). In multivariate analysis, both CSS ($P=0.004$) and GREAT ($P=0.026$) class were significantly associated with failure of radioiodine therapy. The dose of radioiodine did not influence the efficacy of the treatment ($P=0.784$). Patients displaying the highest class in both CSS and GREAT scores had the highest probability to not respond to radioiodine treatment ($P=0.029$).
Conclusions
Both scores can be useful to decide whether the patient may respond or not to radioactive iodine treatment. The concomitant class 3 in both scores likely predicts the inefficacy of radioiodine treatment suggesting in these cases a surgical approach.

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AEP886

Ectopic thyroid tissue presented as left adrenal mass – a case report

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Introduction
Ectopic thyroid tissue is a rare developmental abnormality with the prevalence of 1 per 100.000–300.000 persons in the general population. It is most commonly detected in younger women and presented as lingual thyroid. Here we report a rare case of ectopic thyroid tissue in the left adrenal gland.
Case report
A 29-year old female without previous medical history was incidentally diagnosed with left adrenal gland mass detected on routine abdominal ultrasound check-up. There were no clinical findings suggestive to cortisol or androgen excess. Native abdominal CT scan revealed hyperdense (40 HU) left adrenal gland mass 4.8 × 2.5 cm in diameter, with 7% of relative washout enhancement observed in contrast scans. Abdominal MRI showed T2W phase isodense lesion demonstrating signal loss in T1W phase. Thyroid ultrasonography didn't show any thyroid abnormality. Laboratory findings obtained from thorough adrenal hormonal excess investigation (ACTH, cortisol diurnal rhythm, ODST, aldosterone/PRA, DHEAs, 24 hrs urinary EPI/NOR/DOP) were reported as normal. The patient underwent laparoscopic left adrenalectomy. The intraoperative finding was suggestive to adrenal cyst. Histology of left adrenal mass showed the cyst 15 mm in diameter, with thyroid tissue inside cyst wall. Thyroid tissue had regular cellular characteristic and expressed TTF1, thyroglobulin, CK19, CK7, and PAX8 positivity. Whole body scan with I-131 performed postoperatively didn't reveal any other additional sites of thyroid tissue.
Conclusion
We reported an exclusive case of ectopic thyroid tissue in the left adrenal cystic lesion.

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AEP887

Vitamin D supply influences negatively the serum IL-6 and IL-17A levels in Hashimoto's thyroiditis, while positively the serum antibody levels against thyroid peroxidase and TSH receptor in Graves' disease

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Vitamin D plays an important role in the adaptive and innate immunity besides its skeletal effects. Some autoimmune disease is associated with vitamin D deficiency highlighting its crucial involvement in the onset of autoimmune diseases. This study investigated the relationship between the vitamin D supply and the serum IL-6, IL-17A and antibody levels against thyroid peroxidase (TPO) and TSH receptor in autoimmune thyroid diseases. Serum IL-6, IL-17A and antibody levels against TPO and TSH receptor were measured in 80 patients with autoimmune thyroid diseases (57 cases with Hashimoto's thyroiditis, mean age of 48 ± 14 years and 23 cases with Graves' disease, mean age of 48 ± 25 years, of whom 10 cases had ophthalmopathy). Data were displayed in geometric mean (95% confidence interval). No difference was found in vitamin D levels between the two groups of autoimmune thyroid deseases, but the serum levels in vitamin D deficient patients were significantly higher in Hashimoto's thyroiditis compared with those in Graves' disease [27.72 (10.4–73.91) vs 14.37 (2.53–81.57) nmol/l, $P<0.022$]. Patients with hyperthyroid Graves' ophthalmopathy demonstrated increased vitamin D levels compared with those in euthyroid state [43.87 (28.19–68.26) vs 18.26 (2.98–111.72) nmol/l, $P<0.0467$]. The serum IL-6 [$r=-0.27$, $P<0.0423$] and IL-17A [$r=-0.3335$, $P<0.0113$] levels inversely correlated with the serum vitamin D levels and the vitamin D supply influenced them negatively in Hashimoto's thyroiditis [18.54 (4.33–79.3) vs 8.23 (0.71–95.59) ng/ml, $P<0.0248$ for IL-6 and 10.29 (3.92–27) vs 5.25 (1.44–19.22) ng/ml, $P<0.0031$ for IL-17A levels between the patients with vitamin D deficiency and sufficiency]. The serum anti-TPO ($r=0.7452$, $P<0.0054$) and anti-TSH receptor antibody levels were positively influenced by the vitamin D supply in Graves' disease, particularly in patients without ophthalmopathy [32.17 (3.24–319.28´) vs 394.97 (30.08–5186.02) IU/ml, $P<0.021$ for anti-TPO and 1.54 (0.54–4.39) vs 6.64 (2.86–15.42) IU/l, $P<0.0299$ for anti-TSH receptor antibody levels between patients with vitamin D deficiency and sufficiency]. The above mentioned relationships were also demonstrated by multivariate analysis in generalized linear model (GLM). Conclusions, the vitamin D levels influenced controversially the serum IL-6 and IL-17A levels in Hashimoto's thyroiditis and positively the antibody levels againts TPO and TSH receptor inGraves' disease demonstrating the difference in the activity of the adaptive immunity between these autoimmune thyroid diseases. The vitamin D supply can contribute to ameliorate the effects of inflammatory cytokines and amplify the antibody production against thyroid antigens.

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AEP888

Cumulative effects of thyroid hormones over 10 years and risk of general and abdominal obesity; tehran thyroid study

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Background
Recently many cross-sectional and a few longitudinal studies reported that thyroid hormones even within normal ranges are associated with measures of adiposity. We aim to assess if changes in TSH and Free T4 (FT4) over 10 years of follow-up would be associated with changes in BMI and waist circumference or risk of general and abdominal obesity.
Methods
4179 participants of Tehran Thyroid Study(TTS) who had attended at baseline(1999–2001) and at three subsequent follow-ups every 4 years(up to 2011) were enrolled. At baseline, participants with serum TSH < 0.1 or >10 mU/l, BMI < 18.5 kg/m^2, pregnancy or history of thyroid medication or surgery and missing data were excluded. Finally, data of 2317 subjects remained for the study analysis. The median follow up time was 9.7y. Body weight, waist circumference were measured and serum concentrations of FT4 and TSH were assayed at baseline and three follow-ups. To account for within-subject correlation, the generalized estimating equation (GEE) was usedto assess the association between a1SD change in main exposures(CE.TSH and CE.FT4) and changes in BMI; calculated scores of CE.TSH and CE.FT4 were included in models as a time varying exposure.
Results
Mean age of the study population was 43 ± 13y, of whom 59.7% were women. Cumulative excess of TSH or FT4 were not associated with increased incidence of obesity, overweight and abdominal obesity. However, in over weights, after adjusting for age, sex, smoking, education, physical activity and HOMA-IR, for each standard deviation increase in the CE.FT4(β = –0.23,95% CI : –0.34, –0.11) and CE.TSH(β = 0.13,95% CI : 0.03, 0.22), BMI was changed negatively and positively, respectively[sd(CE.TSH) = 19.27, sd(CE.FT4) = 1.72)]. In GEE analysis, however, a one unit increase in TSH was associated with 0.02 increase in BMI in the total population(β = 0.02, 95% CI : 0.008, 0.03), an increase which remained significant only in women; a one unit increase in FT4 was significantly associated with 1.7 decrease in BMI(β = –1.7.95% CI : –1.9, –1.4) in the total population which remained significant in both sexes after adjusting for age, sex, smoking, physical activity, education and HOMA-IR. After entering both exposures of TSH and FT4 to the model, only FT4 independent of TSH was inversely associated with BMI. The one unit decrease in FT4 was also associated with increase in WC(β = –3.88, 95% CI : –5.09, –2.68) in both genders.
Conclusion
Cumulative effects in thyroid hormones over time indicated no risk for general or abdominal obesity. However TSH alterations in women and FT4 in both sexes were positively and negatively associated with BMI, respectively. FT4 variations could negatively affect WC in men and women independent of insulin resistance and even TSH.

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AEP889

Iodine deficiency and mortality in spanish adults. Di@bet.es study

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Objective
To study the association between the state of iodine nutrition, and the risk of total and cause mortality in a representative sample of the Spanish adult population.
Design
Longitudinal observational study to estimate mortality risk according to urinary iodine (UI) concentrations using a sample of 4370 subjects >18 years representative of the Spanish adult population participating in the national study Di@bet.es (2008–2010). We used Cox regression to assess the association between IU at the start of the study (<50, 50–99, 100–199, 200–299 and ≥300 µg/l) and mortality during follow-up (INE- end of follow-up December 2016) in raw models and adjusted to possible confounding variables: age, sex, educational level, hypertension, DM, Obesity, CKD, smoking, hypercholesterolemia, thyroid dysfunction, diagnosis of cardiovascular disease, cancer diagnosis, Area of residence, physical activity, adherence to Mediterranean diet, dairy intake and iodized salt.
Results
A total of 254 deaths were recorded during an average follow-up of 7.3 years. The causes of death were cardiovascular 71 (28%); cancer, 85 (33.5%) and other causes 98 (38.5%). Compared to the reference category with adequate iodine nutrition (IU 100–300 µg/l) the Hazard Ratios of all-cause mortality in the category with IU ≥300 µg/l was 1.04 (CI 95% 0.54–1.98); however, in the categories with 50–99 IU and <50 µg/l, the Hazard Ratios were 1.29 (95% CI 0.97–1.70) and 1.71 (95% CI 1.18–2.48) respectively (*P* for trend 0.004). Multivariate adjustment did not significantly modify the results.
Conclusions
Our data indicate an excess mortality in individuals with severe iodine deficiency adjusted to other possible confounding factors.

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AEP890

New predictors of response to treatment with intravenous methylprednisolone in thyroid-associated orbitopathy

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Introduction
Thyroid-associated ophthalmopathy is the most frequent extrathyroidal manifestation of Graves' disease. Its treatment is based on the administration of intravenous corticosteroids, and the clinical activity score (CAS), TSH-binding inhibitor immunoglobulin (TBII) and TSH-receptor antibodies (TRAb) have been classically used to measure the response to treatment. However, in recent studies [1] it has been observed that other analytical parameters such as cholesterol and triglycerides could also be related to the response to such treatment.
Methods
A retrospective observational case-control study was performed. We studied 55 patients with thyroid ophthalmopathy who have been admitted to Hospital Clínico Lozano Blesa, in Zaragoza (Spain) in the last 10 years to receive treatment with intravenous infusions of methylprednisolone. From each patient, the previous treatment received for their hyperthyroidism and different variables were taken into account in three key moments: Before the first corticoid infusion, halfway through the treatment (Sixth bolus) and after the twelfth and last bolus. Among these parameters were the CAS (Clinical Activity Score), visual acuity and presence of diplopia, and various analytical parameters (TSH, FT4, cholesterol, LDL, HDL, triglycerides, etc.). The statistical significance has been accepted for values of $P<0.05$.
Objectives
To assess whether there is a relationship between the adequate response to intravenous corticosteroid therapy in Graves' ophthalmopathy and the different analytical parameters previously mentioned.
Results
An increased risk of having poor response to intravenous corticosteroid therapy has been observed in those patients with elevated triglycerides (Odds Ratio (OR) 1.85 [IC95%=1.05–3.28]), smokers (OR 5.05 [IC 95%=1.94–27.19]) and in those with high levels of TSH-binding inhibitor immunoglobulin (OR 5.17 [IC 95%=1.11–24.04]). Moreover, a higher TBII mean (17.4 vs 8.9, $P=0.028$) and a higher triglyceride mean (127 vs 81 mg/dl, $P=0.034$) were found in nonresponders.
Conclusion
There are several factors that can serve as predictors of response to intravenous corticosteroid treatment in thyroid-associated orbitopathy, some of them are already well known, like antithyroid antibodies or smoking, and others started to gain relevance recently, such as cholesterol or triglycerides. Thus, all these factors could be used to classify Graves' orbitopathy patients prior to intravenous corticoid treatment and only start that treatment in the group of patients that could potentially have more benefit from it.

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AEP891

Differentiation of follicular thyroid cancer from follicular thyroid adenoma with sonographic features – results of a meta-analysis

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Introduction
According to the results of several studies and meta-analyses, certain ultrasound features are associated with increased risk of thyroid malignancy. However, most of those research papers included mainly papillary thyroid cancers (PTCs); these results cannot be simply extrapolated for the differentiation of follicular thyroid adenomas and cancers (FTAs and FTCs). The aim of the present study was to perform a meta-analysis of so far conducted research and identify sonographic features suggesting malignancy in case of follicular lesions, potentially differentiating FTA and FTC.
Material and methods
We carried out a meta-analysis following the Cochrane and PRISMA guidelines. We searched PubMed, MEDLINE, Academic Search Complete, CINAHL Complete, CINAHL, Scopus, Cochrane, Health Source: Nursing/Academic Edition, Web of Knowledge, MasterFILE Premier, Health Source – Consumer Edition, Agricola, Dentistry and Oral Science Source databases from January 2006 up to July 2018 to find all relevant, full-text journal articles written in English. The search strategy included Medical Subject Headings terms and keywords: 'thyroid and ('follicular cancer' or 'follicular carcinoma' or 'follicular neoplasm' or 'follicular adenoma' or 'follicular nodule') and (ultrasound or ultrasonography or elastography or 'color doppler' or 'power doppler')'. The pooled estimates of sensitivity, specificity, positive and negative predictive value (PPV, NPV), and odds ratios were obtained from the bivariate model.
Results
After a complete systematic review was performed, 15 studies met the inclusion criteria. They covered analyses of 15209 nodules. The overall odds ratios for particular features giving a FTC risk varied from 1.44 to 10.19. Specificity to predict FTC for individual features varied from 18 to 100%, and the sensitivity ranged from 1 to 94%. NPV was 64–92%, and PPV was 28–96%. The highest overall odds ratio in increasing the risk of malignancy was calculated for tumor protrusion (OR=10.19; 95% CI : 2.62–39.71), microcalcifictions or mixed type of calcifications (micro- and macrocalcifications): 6.10 (3.00–12.50), irregular shape: 5.89 (1.09–31.82), solid or mainly solid structure: 5.22 (1.70–16.05) and marked hypoechogenicity: 4.25 (2.57–7.05). The lowest OR was characteristic for doppler pattern 3 or more: 1.44 (0.76–2.74). The probability of FTA diagnosis suggests the oval or round shape of the lesion, presence of cystic component. Less specific features suggesting benignity are lack of calcifications and visible halo.
Conclusions
The sonographic features associated with malignancy of follicular lesions are distinct from those widely reported for all thyroid cancers, including PTC, and may be a useful tool to guide thyroid nodules management.

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AEP892

Anaplastic thyroid cancer arising froma patient with congenital thyroid dyshormonogenesis; A case report with a novel thyroglobulin gene mutation

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Background
Concomitant thyroid cancer in patients with congenital thyroid dyshormonogesis (TD) is extremely rare and only few cases of differentiated thyroid cancer in patients with TD were reported in literature. We present the first case of anaplastic thyroid cancer (ATC) in woman with TD.
Case
A 46-year-old female patient was referred to our hospital for thyroid surgery due to rapid tumor growing and compressive symptoms. The fine needle aspiration result of a local clinic was follicular neoplasm. She and her two younger sisters had diagnosed as congenital hypothyroidism and received thyroid hormone replacement therapy from childhood. The growth and psychomotor development of three sisters were within normal range. Her serum thyroglobulin (TG) level was not detected and genetic tests for TD were performed for patient and her younger sisters. The targeted exome sequencing revealed compound heterozygous mutations in the TG gene and saner sequencing represented a c.3790T>: C (*P*, Cys1264Arg) mutation located at exon 17 and c.7070T>: C (*P*. Leu2357Pro) mutation at exon 19 in patient and one sister. The c.7070T>: C (*P*.Leu2357Pro) mutation is novel mutation. After total thyroidectomy, she was diagnosed with ATC with lung and bone metastasis. She started Lenvatinib therapy and still alive for 11months after the first diagnosis of ATC.
Conclusion
TD patients are exposed to long term hypothyroid statuswith elevated thyroid stimulating hormone, which make thyroid goiter and nodules. Genetic mutation under chronic stimulation of the thyroid gland could change nodules to aggressive natures. Further investigation is necessary to identify the association between thyroid cancer and TD.

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AEP893

Thyroglobulin measurement in fine-needle aspirates of lymph nodes in patients with differentiated thyroid cancer

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Backgraund
The high incidence of cervical lymph nodes (LNs) metastasis in differentiated thyroid carcinoma (DTC) and lack of effective diagnostic tools determines the need for elaboration more specific tests.
Aims
The aim of our study was to evaluate the accuracy and cut-off point of the thyroglobulin (Tg) in the washout fluid of fine-needle aspiration biopsy (FNA-Tg) in the diagnosis of DTC LNs metastasis.
Materials and methods
A retrospective studyinvolved 245 patients with recurrent DTC and suspicious cervical LNs. All patients were evaluated FNA-Tg, serum Tg levels (sTG), Tg antibodies (TgAb) and thyroid stimulating hormone (TSH). Surgical treatment was performed in 125 patients with malignant changes according to the cytology, high FNA-Tg values, sTg. Patients were divided into 2 groups with reactive ($n=23$) and metastatic ($n=102$) changes in LNs according to the histological examination. FNA for both cytology and FNA-Tg was performed with a 22-G needle. FNA-Tg was aspirated through the needle with a syringe from a test tube with 0.5 ml of normal saline. TSH levels were measured by electrochemiluminescence immunoassay (Architect), reference range 0.25–3.5 mIU/l. FNA-TG, sTg (3.5–77.0 ng/ml), TgAb (0–115 IU/ml) was performed on the automated system Cobas 601 (Roche, France). Clinical and laboratory data were compared using Mann Whitney U test, results are presented as median (25 and 75 quartiles), $P<0.05$. Diagnostic significance and the best cut-off value for FNA-Tg for the malignancy was performed using receiver operating characteristic curve analysis (ROC). All analyses were performed using the SPSSv23 Statistic (USA) and MedCalc v. 18.2.1 (Belgium) software.
Results
All patients were comparable by clinical (sex, age) and laboratory (TSH, sTG, Tg Ab) parameters. The median FNA-Tg in metastatic group was 537.0 [0.1; 1000] ng/ml while in benign group it was 17.9 [0.5; 158.0] ng/ml, $P=0.003$. The sensitivity of isolated FNA was 85%, specificity 57%, AUC=0.618, 95% CI 0.516–0.713. The sensitivity and specificity of FNA-Tg was 73% and 100%, respectively, AUC=0.865, 95% CI 0.78–0.92. The optimal cut-off point for the malignancy was >9.2 ng/ml (sensitivity 75%, specificity 100%), Youden Index 0.73.
Conclusions
Our results showed that additional measurement of the Tg in the washout fluid enhances the sensitivity of isolated FNA in evaluation of DTC lymph nodes metastasis. In our population the cut-off value>9.2 ng/ml can be proposed as a diagnostic threshold for the definition of malignancy.

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AEP894

Association between multifocality and aggressive histopathological findings in papillary thyroid cancer

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Introduction
Papillary thyroid cancer (PTC) is usually tied to an excellent prognosis, with a 10-year disease specific survival rate of 98%. Nevertheless, some clinicopathological features are associated with a worse outcome. Therefore, a precise risk assessment is crucial for the clinicians deciding the most appropriate treatment for each tumour. Multifocal tumours (MFPTC) appear to have be a worse prognosis than unifocal tumours (UFPTC) in some series, but this aspect is disregarded by the American Thyroid Association guidelines for risk stratification on PTC. The following study tries to evaluate a possible association between MFPTC and aggressive histopathological findings.
Material and methods
We designed a retrospective cross-sectional observational study. Data regarding every histologically confirmed PTC (non-aggressive variants) larger than 2 mm operated at our centre between 2001 and 2019 was gathered. We used chi square test to evaluate the association between multifocality and several aggressive histopathological findings: extrathyroidal extension (ETE), lymph node involvement (LNI), BRAFV600E mutation and desmoplastic stromal reaction.
Results
We studied 662 patients with non-aggressive variants of PTC. 651 patients had the ETE described in their pathological reports: 404 UFPTC (19.6% with ETE) and 247 MFPTC (26.3% with ETE). From 639 patients, there were LNI in 170 histological specimens:35.8% of MFPTC (88 out of 246) and 20.9% of UFCPT (82 out of 392). 344 neoplasms had been tested for BRAF V600E mutation: 200 UFPTC (46.5% mutated) and 144 MFPTC (57.6% mutated). In 524 patients the presence or absence of desmoplastic reaction was described in their pathological reports: 308 UFPTC (34.7% with moderate to severe desmoplasia) and 216 MFPTC (46.3% with moderate to severe desmoplasia). There were no differences between groups in sex distribution, age nor tumour size (used largest focus of MFPTC). There was a statistically significant association between the following: MFPTC and ETE [$P=0.04$, OR (CI95%)=1.47 (1.01–2.14)]; MFPTC and LNI [$P<0.0001$, OR (CI95%)=2.11 (1.48–3.02)]; MFPTC and the presence of BRAFV600E mutation [$P=0.04$, OR (CI95%)=1.56 (1.02–2.41)]; and MFPTC and moderate to severe desmoplastic reaction [$P<0.01$, OR (CI95%)=1.62 (1.14–2.31)].
Conclusion
MFPTC are associated with several aggressive histopathological findings:ETE, LNI, BRAF V600E mutation and moderate to severe desmoplasia. Therefore, we suggest that multifocality should be regarded when deciding the treatment of PTC, aiming for more extensive surgical treatment when multifocality is present. The association between MFPTC and aggressive histopathological findings questions the currently proposed surgical approach for intrathyroidal PTC smaller than 4 cm (lobectomy) due to the risk of neglecting evidence of multifocality.

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AEP895

Cervical lymph node metastasis of a thyroid papillary carcinoma resected with detection by technetium99-nanocolloid: About an original case

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Introduction
Cervical lymph node metastases from differentiated thyroid carcinomas occur mainly in the central compartment with an incidence between 20 and 90% (average 60%). The American Thyroid Association considers that the central compartment goes to the unnamed artery thus systematically including level VII to level VI. We report the case of a patient with resected level VII lymph thanks to identification by technetium99-nanocolloid.
Observation
Patient 32-year-old followed for 3 years for papillary thyroid carcinoma initially classified PT2N1bM0 who received an iratherapy treatment with a thyroglobulin (Tg) level at 71.86 ng/ml and post-therapeutic scanning: hyperfication cervical lymphadenopathy. At 3 months post-iratherapy in front of a Tg at 8.10 ng/ml, a cervical ultrasound finds a lymphadenopathy in level VII, whose fine needle biopsy returned carcinomatous with Tg in rinsing liquid highly positive. The TEP-FDG finds this lymphadenopathy without remote localization. The patient is reoperated under detection by iodine 131, unfortunately the lymphadenopathy doesn't fix the iodine, it couldn't be resected. In view of the Tg levels remained high, it was reoperated a third time under detection with in situ injection of technetium99-nanocolloid, the anatomopathological study found 2 lymphe node metastasis infiltrated and the postoperative ultrasound returned without abnormality.
Discussion
The resection of a lymph node metastasis of a thyroid papillary carcinoma by technique of in-situ injection of technetium99-nanocolloid, inspired by the technique of the sentinel node seems to be a new technique which would make it possible to act on lymphe node difficult to access on a neck modified by previous surgery and which no longer fixes iodine.

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AEP896

PTEN-hamartoma tumour syndrome and thyroid nodular disease: 3 case reports

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Introduction
Germline mutations in tumour suppressor gene PTEN cause heterogeneous phenotypes, that comprise the spectrum of PTEN-hamartoma tumour syndrome (PHTS). Manifestations include macrocephaly, developmental delay, cutaneous lesions, intestinal polyposis and increased risk of neoplasms. Thyroid nodules are identified in about 75% of patients and follicular cell-derived cancer affects 35% of cases, some of which diagnosed as early as 7 years old.
Case 1
6 year old boy, with macrocephaly and autism; genetic test revealed a heterozygous mutation in PTEN (c.359C>A – p.Ala120Glu). Thyroid ultrasound (US) at 6.5 years was normal. At 7 years, US showed 3 nodules: in right lobe (RL), 3.3 mm hyperechoic nodule and 5.8 mm hypoechoic nodule; in left lobe (LL), 3.9 mm hypoechoic nodule. TSH and thyroid antibodies were normal. At 9 years, US showed: in RL, 4.7 mm hyperechoic nodule, with irregular margins; in RL-isthmus transition, 9.3 mm hypoechoic nodule; in LL, 5.6 mm hypoechoic nodule. At 10 years and 9 months, fine-needle aspiration cytology (FNAC) of RL-isthmus transition nodule showed FLUS. Thyroidectomy was performed at 11 years; pathology revealed nodular hyperplasia.
Case 2
8 year old boy, with macrocephaly, learning difficulties, mucocutaneous lesions and lipomas; PTEN sequencing revealed a heterozygous frameshift mutation (c.412dup – p.Tyr138LeufsTer42). Thyroid US showed several hypoechoic, regular-margin nodules, the larger in LL with 9 mm; several suspicious lymph nodes. He had normal TSH, but calcitonin 15.2 pg/ml ($N<8.4$). He was submitted to thyroidectomy at 9.5 years; pathology revealed nodular hyperplasia with two follicular adenomas and reactive adenitis.
Case 3
6 year old boy with macrocephaly, developmental delay, intestinal polyposis and iron-deficiency anemia. Genome sequencing revealed a deletion on chromosome 10 (10q23.1q23.31), involving PTEN and BMPR1A genes. At 6 years and 11 months, US showed enlarged thyroid, with no nodules. At 12 years, US showed a RL nodule with 9 mm and two LL nodules, the larger with 9 mm. He had normal TSH and positive anti-thyroglobulin antibodies. FNAC of RL nodule revealed a benign lesion. At 15 years, US showed in RL a heterogeneous nodule with 21 mm; in LL, a hypoechoic nodule with 16 mm, an area of confluent nodules with 36 mm and other multiple smaller nodules; multiple enlarged lymph nodes. He is waiting for thyroidectomy.
Conclusions
PHTS patients must be evaluated annually with thyroid US, starting after diagnosis. The high risk of carcinoma in young age and the diagnostic difficulties due to multiple thyroid nodules often leads to thyroidectomy in suspicious cases.

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AEP897

Discordant thyroid function test in a patient with X-linked adrenoleukodystrophy

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Introduction
Biotin-streptavidin detection method is used in a majority of commercial immunoassay. Biotinylated antibodies (capture antibodies) bind strongly to streptavidin that anchors those antibodies to the solid phase of the assay. Thus, high biotin concentration in the serum interferes with this bond and alters the expected results. Clinical history of patient and additional laboratory test is important for troubleshooting of discordant thyroid function test result.
Case presentation
A 52 years male was referred by an endocrinologist to our laboratory to evaluate clinic-biochemical discordance for thyroid function test. The resultsshowed a thyroid-stimulating hormone (TSH) level of 0.02 µIU/ml (0.35–5.5 µIU/ml) and a free thyroxine (fT4) level of 5.48 ng/dl (0.89–1.76 ng/dl). Similar finding was found in the report issued by second laboratory. TPO antibody, anti-thyroglobulin and TRAb were negative. Patient had normal thyroid ultrasound and low normal uptake in technitium-99 thyroid scan. This discordant TFT results prompted us to investigate for the possible interference in the TSH and fT4 assay. Patient did not have history of previous thyroid disease. There was no family history of similar TFT findings. He was recently diagnosed with X-linked adrenoleukodystrophy based on findings of long chain fatty acid test after his complaints of progressive weakness and stiffness of lower limb. For his illness, he was taking low dose hydrocortisone and was under trial of high dose biotin. Thus, biotin interference as a cause of discordant laboratory finding was suspected. We reviewed the results of previous TFT and consulted with the clinical laboratories about the design of their immunoassay. Initial results of TSH and fT4 were obtained from Vitros 3600 immunoassay. The second result was from Roche Diagnostics Modular E170. These both immunoassay systems used biotin to label the reaction. We repeated TFT in Siemens, Advia Centaur which used acridinium ester to label the reaction. The results obtained were normal. Hyperthyroidism was ruled out and high dose biotin interference was confirmed.
Discussion
The excess free biotin in sample saturates the streptavidin binding sites preventing adherence of the signal bound antibody–antigencomplex in a non competitive assay (e.g. TSH). This creates a falsely lowered TSH result by decreasingthe signal detected. For fT4 level, a competitive immunoassay principal is used where high biotin concentration causes reduction in light generated and has positive interference with fT4 assay. When an immunoassay with no biotin is used (e.g.Siemens Advia Centaur), the interference disappears.

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AEP898

Age and sex-specific TSH upper-limit reference intervals in the general French population: There is a need to adjust our actual practices

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Background
The increasing age of the general population represents a new challenge for endocrinologists and caregivers since it is well know that the occurrence of thyroid dysfunction increases with age. It is still controversial whether or not reference values of thyrotropin (TSH) adapted to age and sex need to be used. Herein, we aimed to determine reference intervals, in males and females, suitable for thyroid disease exploration and follow-up during adult life in a tertiary center in France.
Methods
Over 11 years, 295775 TSH were measured in a single lab that used the same TSH reagent during this period. Among the 156025 TSH results available for analysis, 90 538 values were from female subjects, 82019 were from patients aged >60 years and 26825 aged >80 years. By using an indirect approach, we determined references values of TSH adapted to age and sex, and we then evaluated the proportion of patients who would have been reclassified with these reference values.
Results
The median TSH ranged from 1.2 to 1.4 mUI/l during the study period. The circannual range of the upper limit of the reference value was 4.6 to 5.4 mUI/l. By contrast, the upper limit of reference range of TSH increased with age; in females the median to 97.5th percentile values increased continuously with age from the age of 30 years to the oldest age group (90–108 years). Using new calculated reference values in patients with TSH above the conventional upper limit reference value (4 mUI/l), the proportion of results reclassified as physiologicalranged, according to age-group, from 26.3 to 65.1% in females and from 13.6 to 37.7% in males; in among those aged >60 years, 50.5 to 65.1% of females and 33.0 to 37.7% of males were reclassified.
Conclusions
The use of TSH age-specific and sex-specific upper-limitreferences values led to the reclassification of a great number of samples, notably among women. This suggests that age-specific TSH upper-limitreference intervals in daily practice should be used in order to avoid misclassification.

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AEP899

Thyroid hormone regulation of brain metabolism: Study in an animal model of the co-occurrence of depression and hypothyroidism

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Objective
Thyroid hormones are required not only for central nervous system development in the early stages of life but also play a key role in the maintenance of adult brain function. It is known that in adults, thyroid diseases can lead to various clinical manifestations i.e affective disorders, depression, memory impairment. The effects of hypothyroidism on brain functions seem particularly pronounced in depression, but until now, the mechanism underlying this relationship has not been fully understood.
Aim
The goal of the present study was to determine the effects of hypothyroidism on the brain glycolysis, citric acid cycle and oxidative phosphorylation processes in an animal model of depression.
Methods
Study was performed in an animal model of endogenous depression (Wistar-Kyoto rats) and model of coexistent depression and hypothyroidism (6-n-propyl-2-thiouracil – PTU- treatment). PTU (0.05%) was administered in drinking water for 3 weeks. The behavioral tests, enzyme-linked immunosorbent assays, colorimetric methods, immunoblots, and high-resolution respirometry were applied to investigate the changes in selected metabolic markers in the frontal cortex and hippocampus. After behavioral verification animals were sacrificed under nonstressful conditionsto dissect frontal cortices and hippocampi. The results were analyzed using the STATISTICA 13.3 software. A p-value <0.05 was considered to be significant.
Results
The applied model was verified behaviorally and hormonally. It was observed that in the model of co-occurrence of depression and hypothyroidism the pyruvate concentrations in the frontal cortex and hippocampus were downregulated and the lactate level in the hippocampus was reduced. Moreover, in the hippocampus, the aconitase activity was increased. The levels of electron transport chain complexes and pyruvate dehydrogenase activity in the frontal cortex were reduced. In the functional study, conducted with high-resolution respirometry the alternations in the oxidative phosphorylation processes in the hippocampus were demonstrated.
Conclusions
Obtained data indicate an important impact of thyroid hormones on brain metabolism in the course of depression. Furthermore, the hypothalamic-pituitary-thyroid axis hypoactivity increases brain metabolic changes observed in the model of endogenous depression. Changes in the frontal cortex may result from an observed decrease in the expression of thyroid hormone receptor alpha-1 and/or D2 deiodinase downregulation. It also seems that metabolic changes in the hippocampus may be one of the causes of long-term potentiation reduction and synaptic plasticity impairment.
Acknowledgments
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AEP900

Severe toxic reaction on thiamazole in a patient with hyperthyreoidism

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Female patient (56 y) with hyperthyroidism (start TSH 0.01 mIU/l; fT3 15.8 pmol/l; fT4 39.4 pmol/l) one month after initiation of thiamazole therapy (10 mg 3 × 1/1 week, then 2 × 1) came to the emergency room with symptoms of sweating, palpitations, nervousness, itching, fever (37.6 C), icterus. In medical history: oesophageal achalasia surgery 5 years ago, non-smoker. Therapy: thiamazole, bisoprolol, alprazolam. Initially in laboratory findings: leukopenia (L 1.2 × 109/l), liver lesion (total bilirubin 196 µmol/l, AST 71 U/l, ALT 69 U/l, ALP 558 U/l, GGT 379 U/l) and elevated CRP (183.4 mg/l). During hospitalization a progression of pancytopenia (L 0.7 × 109/l), worsening of the liver lesion and CRP (total bilirubin up to 267 umol/l, ALP 294 U/l, GGT 153 U/l, CRP 346 mg/l) were recorded. TSH was 0.01 mIU/l with elevated fT3 10.6 pmol/l and fT4 42.7 pmol/l. Abdominal ultrasound found no signs of bile duct obstruction, there was visible splenomegaly. Gastroscopy found gastritis and oesophageal mycosis, acute tonsillopharyngitis. Cytological analysis of the bone marrow showed poor cellular bone marrow with marked neutropenia. Haemocultures, urinocultures, markers of hepatitis and serology EBV IgM were negative. She was treated with antibiotic therapy piperacillin+tazobactam, later replaced with vancomycin+meropenem+fluconazole. Despite antibiotics, filgrastim and symptomatic therapy hyperbilirubinemia persisted, leukopenia and synthetic liver function were worsening. She was transferred to a tertiary institution for further treatment, without the criteria for inclusion on the liver transplant list. Sixteen days after initial hospitalization, J-131 therapy was performed (296 mBq/8 mCi), then lithium carbonate 150 mg 1 × 1 was added to therapy for several months; euthyroidism was achieved. Sixteen months after the described toxic reaction to thiamazole, mild hyperthyroidism was noticed, followed by spontaneous euthyroidism, with a negative finding of scintigraphy and no need for therapy. In conclusion: thionamides are the most common initial therapy for hyperthyroidism. A toxic reaction is also possible with low doses of thiamazole. Regular follow up of thyroid test is required.
Keywords: thyrotoxicosis, thiamazole, toxic liver lesion.

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AEP901

How various doses of iodine effect on thyroid gland in pregnant and lactating women, on the example of regional studies in russian federation?

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Relevance
Question of standards of iodine intake in pregnant and lactating women remains relevant.
Aim of study
to determine status and function of thyroid gland in pregnant and lactating women with and without antibodies to thyroid gland, on the background of taking different doses of iodine in 3 different regions of Russia with different iodine status.
Materials and methods
This study included 414 women in the different trimester of pregnancy (18–42 y.o.) and 256 newborns. They were divided into 2 groups: 1st group – women, receiving potassium iodide 200 mg/day, newborns breastfed from these women; 2nd group – women and newborns, receiving 300 mg/day.
Results
Initially, in all three regions, median iodinuria was below the threshold level (150 µg/l). After 3 months, a significant increase in the level of iodinuria in group 2 (96 µg/l at baseline and 259 µg/l at 3 months) was noted. Against the background of taking different doses, there was no increase of Anti-TPO. When comparing the iodine content of infants who are breastfed, there were no significant differences between the groups. Normal concentration of iodine in the urine was 58.6% in the newborns in the first group and 71% in the second group. The levels of TSH of newbornswere not statistically different; there were no increase above 5 mU/l.
Conclusions
We can say that in order to achieve optimal iodinuria, level of iodine intake should correspond to at least 250 µg/day. For now, initial urinary excretion of iodine does not correspond to normal iodine supply, which indicates the need for preconception treatment in regions with proven iodine deficiency.
Study was carried out by RSF grant N17-75-30 035.

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AEP902

Association between lipid and thyroid function parametersin premenopausal euthyroid healthy women and women on levothyroxine replacement therapy

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Introduction
The relationship between thyroid function tests and lipid parameters is still under hot discussion. According to current recommendations thyroid stimulating hormone (TSH) levels should preferably be below 2.5 mIU/l in healthy women of childbearing age as well as in women on levothyroxine treatment.
Aim
To compare lipid levels and atherogenic indices in premenopausal euthyroid healthy women and women with autoimmune thyroiditis (AIT) on levothyroxyne replacement therapy according to TSH values and evaluate their association with thyroid function tests.
Patients and methods
56 women with AIT and 195 healthy premenopausal women aged 18–40 years were included in the study. Serum levels of TSH, free thyroxine (FT4), total cholesterol, HDL and triglycerides were measured; LDL values were calculated using Friedewald formula. Castelli risk index I (CRI) and II (CRII), atherogenic coefficient (AC) and atherogenic index of plasma (AIP) were calculated. All women were euthyroid with TSH levels between 0.4–4.2 mIU/l and FT4 levels within the reference range (7.86–14.40 pmol/l), not taking steroids, metformin, lipid lowering medications or estrogen containing drugs.
Results
42.9% of the women with AIT had TSH ≥ 2.5 mIU/l compared to 28.7% of the healthy women ($P=0.052$). FT4 levels in women on levothyroxine replacement were higher than in the healthy women in both groups according to TSH levels. No differences between lipid parameteres and atherogenic indicis were found in healthy women and those on levothyroxine with TSH < 2.5 mIU/l. In the group with TSH≥ 2.5 mIU/l healthy women hadelevated levels of total cholesterol more frequently than those with AIT (51.8% vs 20.8%, $P=0.013$). In women with AIT TSH levels did not show any relation to the lipid parameteres, but there was a significant negative correlation between FT4 and total and LDL cholesterol ($P<0.01$) and I1, I2 and AC ($P<0.05$). In healthy women TSH was associated neither with lipid levels nor with atherogenic indicis. However FT4 showed significant negative correlation with HDL levels ($P<0.01$) and positive with I1, I2, AC ($P<0.05$).
Conclusion
Our results suggest that FT4 levels have different impact on lipid metabolism in healthy women and women with AIT. Whether this finding is associated with clinically significant increase in cardiovascular risk and whether intervention is reasonable remains a matter of further investigation.
Keywords: autoimmune thyroiditis, thyroid stimulating hormone, free thyroxine, lipid parameters, atherogenic indicis.

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AEP903

The effect of ramadan fasting on thyroid function tests: A study of patients on thyroxine replacement therapy

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Background
Ramadan fasting entails abstinence of food and drink from dawn to sunset for 30 days. Medication timing also changes; for patients with hypothyroidism this can be a challenge as levothyroxine (LT4) is normally taken on an empty stomach and at least half an hour before breakfast. Complying with this advice during Ramadan is impractical for religious and social reasons. Adverse changes in thyroid function in patients with hypothyroidism have been observed. Whether and for how long these changes persist after Ramadan is unclear.
Aim
Investigate the short and long-term impact of Ramadan fasting on thyroid function of patients on thyroxine replacement therapy.
Methods
Patients with hypothyroidism who attended Imperial College London Diabetes Centre (ICLDC, Abu Dhabi) during 2012 and 2017, and were; (1) Arab-Emirati; (2) aged ≥ 18 years; (3) on LT4; (4) not diagnosed with type 1 diabetes; (5) had a thyroid function test (TFT) within 3 months before Ramadan (BR); and (6) had a TSH result ≤ 10 uIU/ml at that visit (BR), were initially included. Selected patients were then followed up to check if they had a TFT at; (1) 1–2 weeks post Ramadan (PR1); (2) 2–3 months post-Ramadan (PR2); and (3) 4–6 months post Ramadan (PR3). Mann-Whitney test was used to test for significant differences in TSH, FT3, and FT4 levels at BR, compared to PR1, PR2, and PR3.
Results
197 had a TFT at all 4 timepoints (BR, PR1, PR2, and PR3), and were included in the analysis. 89.9% of the cohort studied were females and the mean age was 44.7 ± 12.3 years. Prevalence rates of prediabetes and type 2 diabetes were 33.5% and 9.1%, respectively. At PR1, TSH levels were significantly higher, and FT3 and FT4 levels were significantly lower, compared to BR (Figure 1). These significant differences disappeared at PR2, and PR3, where TSH levels decrease and FT3 and FT4 levels increase.
Conclusions
Ramadan fasting leads to adverse, but temporary changes in thyroid function in patients with hypothyroidism which resolve within 2–3 months after Ramadan. Further prospective studies are needed to establish appropriate timing for thyroxine ingestion during Ramadan.

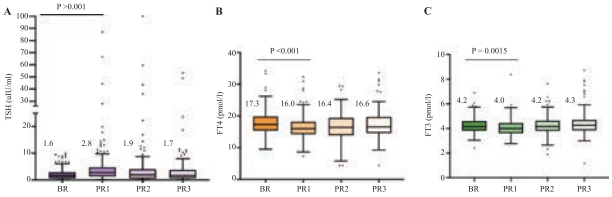

Figure 1 The impact of Ramadan on thyroid function tests. Box plots demonstrating levels of (A) TSH, (B) FT4, and (C) FT3, at within 3 months before Ramadan (BR), 1–2 weeks (PR1), 2–3 months (PR2), and 4–6 months (PR3) after Ramadan.

Numbers above each boxplot represents the median. *P* value; Related-Samples Mann-Whitney Test.

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AEP904

Non-thyroidal illness syndrome in patients admitted for acute disease and its relationship to survival

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Introduction
Non-thyroidal illness syndrome or low T_3 syndrome is an alteration of thyroid hormone levels which occurs as a reaction to acute disease. It is characterized by low TSH levels and low T_3 and T_4 levels. It is transient. The severity of its expression may be related to the severity of the acute disease. It affects patients hospitalized for acute disease in the department of medicine or surgery and in the acute care unit.
Aim
The aim was to study the expression of non-thyroidal illness syndrome and its relationship to survival in the department of medicine in a general hospital in a cohort of patients hospitalized for an acute disease.
Methods
In patients hospitalized for an acute disease after admission to the department of medicine in a general hospital the levels of TSH, T_4, T_3, freeT_4 and freeT_3 were measured over a period of a calendar year. The patients were followed up until exit from the hospital or death. In the department of medicine 831 patients were admitted with acute disease during the period of a calendar year.
Results
Within this group of 831 patients, 230 patients were found to have non-thyroidal illness or low T_3 syndrome. TSH levels were lower in the group of patients with non-thyroidal illness syndrome as opposed to those who did not express the syndrome, 0.52±0.17 μIU/mlas opposed to 2.81±0.34 μIU/ml ($P<0.001$, Student's t test).T_3 levels were lower in the group of patients with non-thyroidal illness syndrome as opposed to those without the syndrome, 0.52±0.049 ng/ml as opposed to 0.57±0.036 ng/ml ($P<0.001$). T_4 levels were lower in those with the syndrome as opposed to those without the syndrome, 4.72±0.77 μg/dl as opposed to 6.53±0.43μg/dl ($P<0.001$). FT_4 levels were 1.058±0.18 ng/dl in the patients with non-thyroidal illness syndrome as opposed to 1.01±0.15 ng/dl in those without it. The probability of death was found to be higher in the group with the non-thyroidal illness or low T_3 syndrome (chi-square test with Yates correction 7.7593, $P=0.005344$).
Conclusion
It appears that the non-thyroidal illness or low T3 syndrome is frequently observed in patients in the department of medicine, who are hospitalized for acute disease of varying etiology. In the cohort described herein the expression of non-thyroidal illness syndrome was found to be related to increased probability of death.

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AEP905

Spurious thyroid function test results due to interference: Consider concealed biotin in health supplements

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Biotin is used in many hormone immunoassays as an immobilizing system as streptavidin binds biotin with high affinity. Recently, cases with spurious results from biotin interference have been increasing due to widespread use of vitamin supplements containing biotin. We report two cases of erroneously high total T3 levels caused by biotin interference.
Case 1
A 88-year-old female who had total thyroidectomy for papillary thyroid cancer 10 years ago and had been taking levothyroxine 125 μg/day underwent routine follow-up thyroid function tests (TFT). Surprisingly, her serum total T3 was >651 ng/dl (60–160) and TSH 0.65 μIU/ml (0.4–4.8). Hormones were measured with a chemiluminescent immunoassay (Cobas: Roche Diagnostics, West Sussex, UK). She had no symptoms and signs of thyrotoxicosis. Subsequent detailed history revealed the culprit. Vitamin supplement (Adult multivitamin Gummies, Kirkland Signature, US) she had been taking since several months ago contained 300 μg biotin per tablet. Her serum total T3 level normalized to 110 ng/dl 1 week after stopping the vitamin.
Case 2
A 43-year-old female who had left lobectomy for papillary thyroid cancer 9 years ago and no levothyroxine replacement underwent routine follow-up TFT. Although she had no signs of thyrotoxicosis, her serum total T3 was 633 ng/dl, free T4 2.42 ng/dl, and TSH 0.786 μIU/ml. She had been taking several complex health supplements including vitamins, probiotics and diet products. Biotin was not identifiable in the label on the products. Repeated TFT results was normalized 1 week after stopping all supplements.
Biotin interference should be considered when TFT results are not compatible with clinical findings, because biotin use is widespread, and some health supplements contain concealed biotin. If biotin interference is suspected, repeating the TFT after stopping biotin supplement for one week can be a reasonable approach.

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AEP906

The effect of selenium supplementation and gluten-free diet in patients with subclinical hypothyroidism affected by autoimmune thyroiditis

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Introduction
Ongoing scientific research indicates that there is a dangerous link between eating foods that contain gluten and Hashimoto's thyroiditis (HT). Gluten can be an irritant to HT by creating inflammation in the thyroid gland. Selenium, an important oligoelement, is a component of the antioxidant system. Over the last decade, it has been ever more frequently discussed in the context of thyroid disorders. The purpose of this study was to highlight the positive response of Hashimoto's patients with subclinical hypothyroidism (SH) treated with Se and gluten-free diet in restoring a normal thyroid function.
Methods
A total of 98 drug-naive women (mean age 39.60±7.36 years) with HT having Thyroid Stimulating Hormone (TSH) levels between 4 and 8 μIU/ml and normal free thyroxine (fT4) and free triiodothyronine (fT3) levels, were randomized into 2 groups: group A ($n=50$) receiving 200 μg selenium in the form of L-selenomethionine orally and gluten-free diet for 6 months and group B ($n=48$) selenium alone without any dietary treatment. Serum titers of thyroid peroxidase (TPOAb) and thyroglobulin antibodies (TgAb), as well TSH, FT4, FT3 were measured at the beginning of the study and 6 months later.
Results
At the end of the study, euthyroidism was restored in 37/50 (74%) of group A participants, and in 28/48 (58.3%) of group B participants. TSH, TPOAb and TgAb levels were significantly reduced in both group after six months of treatment. Serum TPOAb titer in group A had a more significant decrease (by 49%) than those in group B (by 34%).
Conclusions
The results suggest that the gluten-free diet with selenium supplementation is more effective in reducing of TSH, TPOAb and TgAb levels by comparing selenium supplementation alone in Hashimoto's women with SH.

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AEP907

Iodine sufficiency among school age children of Minsk region (Belarus) in 2018

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Background
The problem of iodine deficiency in Belarus remains topical, due to the historical understanding of iodine deficiency in the environment. As a result,

the Republic of Belarus has developed and since 2000 implemented a strategy for iodine deficiency elimination, based on the use of iodized salt and food fortification.
Aims
To determine iodine status in children living in Minsk region.
Materials and methods
The study included 150 school children aged 9–12 years of both sexes. Questioning, determination of urinary iodine concentration and thyroid volume with ultrasound were carried out.
Results
Urine Iodine Median was 186.5 μg/l in the 150 children in Minsk region of Belarus. Thyroid volume corresponds to the normative values in children. Data are presented in the table. Thyroid volume (ml) in children depending on age According to the survey, 78.8% of households used iodized salt.

Gender	Age, y.o			
	9	10	11	12
Girls	4.288 (n=17)	5.385 (n=21)	5.701 (n=19)	5.885 (n=17)
Boys	4.267 (n=20)	5.060 (n=20)	5.763 (n=18)	6.528 (n=18)

Conclusions
The use of iodized salt and foods allows an adequate level of iodine supply in schoolchildren.

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AEP908

The use of different sodium/potassium perchlorate regimes could affect response time in the treatment of amiodarone-induced thyrotoxicosis

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Introduction
In the treatment of amiodarone-induced type I or mixed thyrotoxicosis, sodium or potassium perchlorate is often associated to thionamides, when the latter are insufficient for a prompt control of thyroid hormone secretion. Perchlorate competes with iodine for entrance into the follicular cell, and also induces a discharge of iodine from these cells with each administration. We compare the effect of 3 different regimes of perchlorate with methimazole on control of fT4 secretion.
Methods
Retrospective. 41 patients were treated by Endocrinology of a tertiary hospital for amiodarone –induced thyrotoxicosis (AIT) with potassium/sodium perchlorate associated to methimazole (30 mg/day) over an 11-year period. Diagnosis of type I or mixed AIT was based on thyroid doppler ultrasound, fT3/fT4 ratio, MIBI scan, IL-6 levels, and response to therapy. Patients with mixed AIT initiated perchlorate following inadequate response to glucocorticoid therapy and/or methimazole. Patients with suspected type I initiated treatment with methimazole alone or combined with perchlorate. 3 perchlorate regimes were used: Group I: 150 mg 6 ×/day, Group II: 200 mg 5 ×/day, Group III: 300 mg tid, maximum of 6–8 weeks. Response was compared, analyzing the number of days necessary for initiation of a sustained fT4 descent (minimum initial descent: 2 pg/ml). [Interquartile range].
Results
26 (63.4%) men, mean age 73 (s.d.:11.7). Type I AIT: 9/41 (22%), mixed: 31/41 (75.6%), Type II 1/41 (2.4%). 5 patients were not included in the analysis: 1 patient receiving 100 mg 4 ×/day, 1 who did not take medication, 1 initially on expired perchlorate, 1 non-responder until switched from propylthiouracil to methimazole, 1 lost to follow-up. The response rate of the remaining patients was analyzed: 10 (27.7%) in Group I, 21 (58.3%) in Group II, and 5 (13.9%) in Group III.
Median baseline fT4 was 39.3 pg/ml [30.1–45.2], 24.2 [20–40.5), and 34.5 [20.4–41] in Groups I, II, and III respectively. Median duration of perchlorate therapy was 42 days [23–45]. Median number of days for response was significantly different among groups, with 3 [2–6], 7 [4–12], and 7 [4–25] in group I, II and III respectively, P=0.015. No significant side effects were observed.
Conclusions
The frequency of perchlorate administration could perhaps play a role in response time in amiodarone-induced type I and mixed thyrotoxicosis, with a more prompt response when perchlorate is administered more often. These results indicate a need for prospective trials, with larger number of patients, designed to compare the effect of different perchlorate regimes.

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AEP909

Plasma levels of Th17 associated cytokines in patients with autoimmune thyroid disease

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Introduction and aim
Cytokines play a crucial role in modulating immune response in both Hashimoto's thyroiditis (HT) and Graves' disease (GD). They may contribute to drive the autoimmune response skewing toward the Th17 phenotype and away from Th1 or Th2 phenotypes. Recent studies revealed an essential role of Th17 cells and their cytokines in the development of autoimmune thyroid diseases (AITD). However, participation of Th17 cells in the pathogenesis of GD is less evidenced. We aimed to assess the balance of Th17 immune response by analyzing plasma levels of Th17 associated cytokines in AITD patients.
Materials and methods
Fifty-four subjects were recruited into this study: 11 treatment naïve, newly diagnosed hyperthyroid GD patients, 30 patients with newly diagnosed euthyroid HT (4 out of 30 patients had mild subclinical hypothyroidism (TSH≤6 μIU/ml)), and 13 age and sex-matched healthy subjects as controls. Cytokine patterns included following groups: Th17 cytokines – IL-17, IL-22; Th17-promoting cytokines – IL-23, IL-10 and IL-6. Plasma levels of cytokines were analyzed in all 54 participants. EDTA plasma immunological markers were detected by xMAP technology (Magpix system; Luminex Corporation, USA). All tests were performed in accordance with the manufacturer's instructions (Cat#: HTH17MAG-14K; Kit Lot#: 3323752; Milliplex).
Results
The mean age of patients was 44.36±15.41 years (28–72 years; nine females and two males) in GD group, 38.55±12.54 years (23–64 years; 29 females and one male) in HT group, and 36.36±11.91 years (22–58 years; 12 females and one male) in controls. Plasma IL-17 and IL-22 levels were 13.90 (10.26, 18.31) pg/ml, 0.04 (0.01, 0.35) ng/ml in HT group, 13.53 (10.34, 16.72) pg/ml, 0.13 (0.01, 0.25) ng/ml in GD group and 17.30 (12.23, 21.06) pg/ml, 0.18 (0.04, 0.51) ng/ml in controls, respectively. Median concentrations of IL-23, IL-10 and IL-6 were 2.42 (1.30, 3.68) ng/ml, 9.71 (5.96, 11.42) pg/ml, 3.12 (0.63, 14.18) pg/ml for HT patients, 2.32 (1.71, 3.36) ng/ml, 9.51 (6.55, 11.12) pg/ml, 6.93 (0.63, 24.90) pg/ml for GD patients and 3.30 (1.96, 4.21) ng/ml, 12.75 (7.63, 16.73) pg/ml, 11.29 (1.30, 15.67) pg/ml for controls, respectively. No significant difference was found between plasma levels of cytokines among the three groups.
Conclusions
Despite recent data on involvement of IL-23/IL-17 axis in the development of thyroid autoimmunity, we did not find any significant differences regarding plasma levels of Th17 associated cytokines between patients with AITD and control group.
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AEP910

The use of single dose of rituximab in combination with radiotherapy, in the treatment of Graves' Orbitopathy – clinical observations

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The treatment of orbitopathy in the course of Graves' disease (GO, Graves' Orbitopathy) still remains a serious therapeutic challenge. Modification of risk factors is considered to be the most important and the most effective method of treatment of benign GO. Treatment with intravenous glucocorticosteroid preparations remains the first-line therapy for moderate- to severe GO but is insufficient in some patients. Radiotherapy has been used in active GO therapy for decades, but its place in the treatment remains undetermined. High hopes are associated with the administration of low doses of rituximab (RTX) – a monoclonal antibody against CD20 antigens presented by lymphocytes B. The aim of the study is to present our clinical experiences in the use of RTX in a single dose in combination with radiotherapy in patients with active orbitopathy where other available forms of treatment were exhausted. Between 2017 and 2020 a group of 8 subjects aged 35–73 with active, moderate to severe GO, not responding to methylprednisolone therapy, was included in treatment. Patients were euthyroid, L-thyroxine supplementation was used if necessary. All patients denied smoking. The follow-up period ranged from 1 to 34 months. While all of the contraindications were excluded, each patient was given a single dose of 500 mg of RTX in a slow continuous intravenous infusion, strictly according to the therapeutic protocol. There were no side effects seen, both during, and after the drug administration. After the pharmacological treatment, each of the patients was referred to a radiotherapy center, to undergo a cycle of ten fractions of the orbit radiation therapy. As the therapy was finished, a hormonal, ophthalmological and imaging reassessment was carried out. There was a significant improvement seen in patients, concerning the clinical activity score (CAS). That included the total deactivation of the inflammatory process in 62.5% of patients. The massive effect of drug administration on the decrease of TRAb level was observed. (mean 23.08 IU/l before and 18.36 IU/l after therapy). MR imaging showed a decrease in eye muscles' thickness. Our experiences with the use of single dose of RTX combined with radiotherapy indicate an efficacy of this new form of second-line treatment of GO. The reduction of activity of orbitopathy in all patients undergoing the treatment and, in some cases, its complete deactivation is very promising. Moreover, the lack of complications during the drug administration as well as the lack of infusion-related complications indicate the safety of the therapy.

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AEP911

Insulin resistance, lipid profile and low-grade inflammation in Hashimoto thyroiditis

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Background
Hashimoto thyroiditis (HT) is the most common autoimmune disease and patients may present different levels of thyroid dysfunction. The association between hypothyroidism and cardiovascular events is well established. However, it remains unclear how mild thyroid dysfunction, autoimmunity and chronic inflammation in HT contribute to an increased cardiovascular risk in euthyroid patients and in subclinical hypothyrodism. Therefore, this study aims to assess insulin resistance, lipid panel and low-grade inflammation in HT patients.
Methods
A total of 228 patients with HT were enrolled and divided into 3 groups, accordingly to TSH levels – TSH 0.35–2.49 µUI/ml, TSH 2.5–4.94 µUI/ml and TSH>4.94 µUI/ml. We assessed thyroid function tests, thyroid antibodies, lipid profile, insulin resistance indexes [homeostasis model assessment insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), insulinogenic index (IGI), whole body insulin sensitivity index (WBISI) and hepatic insulin sensitivity index (HISI)], high-sensitivity C-reactive protein (hs-CRP), vitamin B12, folic acid and homocysteine. Statistical analysis was made using one-way ANOVA, Student's t-test, Pearson's correlations and multiple linear regression.
Results
93.9% of our population were women and mean age was 47.06±15.4 years. No significant statistical differences were found between groups, regarding age, sex and body mass index. The group TSH>4.94 µUI/ml, in comparison to the group TSH 2.5–4.94 µUI/ml, showed significant higher values of HOMA-IR (3.77±2.93 vs 1.95±1.25, $P<0.001$) and inferior values of QUICKI (0.48±0.13 vs 0.70±0.39, $P=0.049$) and HISI (41.73±29.03 vs 79.84±63.72, $P=0.026$). The group with TSH 2.5–4.94 µUI/ml, in comparison to the group TSH 0.35–2.49 µUI/ml, presented significant higher levels of Apolipoprotein B (ApoB) (102.14±33.885 vs 97.64±21.001, $P=0.036$). In the total group, positive correlations were found between TSH and both triglycerides ($r=0.206$, $P=0.002$) and HOMA-IR ($r=0.209$, $P=0.002$). Positive correlations were found between thyroid peroxidase antibodies levels and total cholesterol ($r=0.166$, $P=0.013$), LDL-cholesterol ($r=0.173$, $P=0.01$), triglycerides ($r=0.148$, $P=0.027$), ApoB ($r=0.190$, $P=0.006$) and HOMA-IR ($r=0.141$, $P=0.033$). Thyroglobulin antibodies correlated positively with triglycerides ($r=0.140$, $P=0.036$). Hs-CRP correlated positively with IGI ($r=0.156$, $P=0.024$) and negatively with WBISI ($r=-0.177$, $P=0.010$).
Conclusions
HT patients with mild thyroid disfunction present a more atherogenic lipid profile and higher resistance to insulin action. Thyroid autoimmunity also seems to be related to insulin resistance, to a less favorable lipid panel and low-grade inflammation. These findings demonstrate the importance of screening for cardiovascular comorbidities in these patients to provide an early diagnosis and better treatment decisions.

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AEP912

Thyroid arterial embolization for refractory amiodarone-induced thyrotoxicosis in a patient with congenital heart disease

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Introduction
Amiodarone-induced thyrotoxicosis (AIT) in patients with congenital heart disease (CHD) has an estimated cumulative incidence of 13–21%, and prompt reversal to euthyroidism is crucial in these patients. We present a case of refractory AIT in a patient with CHD who was treated with thyroid arterial embolization (TAE).
Clinical case
A 34-year-old male with complex cyanotic CHD (great vessels transposition, interventricular communication), had palliative cardiac surgery in his childhood and developed heart failure (HF), pulmonary hypertension, and supraventricular tachyarrhythmias. Since 2013 he was treated with amiodarone with no adverse effects. In April 2019 he was referred to our Endocrinology Department due to thyrotoxicosis, which was detected due to worsening of HF and weight loss, irritability and tremor of the extremities with 4 months of evolution. He had TSH 0.02 uIU/ml [0.35–4.94] FT4 2.12 ng/dl [0.70–1.48] FT3 5.86 pg/ml [1.88–3.18]. Analytical reassessment at 1st visit: TSH<0.01 mIU/l FT4 4.60 ng/dl FT3 14.57 pg/ml, TRAB negative. He started therapy with thiamazole 30 mg/day and prednisolone 40 mg/day. Despite a favorable initial response, the clinical and analytical condition deteriorated – ventricular tachyarrhythmia with implantable cardioverter-defibrillator placement – requiring multiple admissions, increasing doses of thiamazole (60 mg/day) and glucocorticoids (dexamethasone 10 mg/day) and initiation of cholestyramine 24 g/day and lithium 800 mg/day. On the 4th month of follow-up, due to failure of medical therapy, thyroidectomy after plasmapheresis was considered, but both were contraindicated by the patient's cardiac condition. After multidisciplinary team discussion, it was decided to perform TAE of the 4 arteries with polyvinylalcohol particles 250–300 microns, using hybrid imaging with angiography and computed tomography. There were no complications and gradual clinical and analytical improvement was obtained. On the 14th week after the procedure, the patient reached normal thyroid function on lower doses of anti-thyroid drug and no need of glucocorticoid.
Conclusion
This case was challenging, not only because it was urgent to control thyroid function due to cardiac deterioration, but also because thyroidectomy was contraindicated and AIT was refractory to medical treatment. TAE is rarely employed in AIT, but has proved to be the only therapeutic option in this patient, solely possible in a center with experienced interventional radiology unit.

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AEP913

Effect of increased levothyroxine dose on depressive mood in older adults undergoing thyroid hormone replacement therapy

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Background
Depressive mood consequent to hypothyroidism can be reversed with levothyroxine (LT4) replacement therapy. However, it is unclear whether increasing LT4 dose confers additional mood benefits.
Methods
This was a single-blind before-and-after study of 26 patients with hypothyroidism who were aged 65 years or older and undergoing LT4 replacement therapy. Geriatric Depression Scale (GDS-K) and Hyperthyroid Symptom Scale (HSS-K) were assessed at baseline, 3 months after increasing LT4 dose by an additional 12.5 µg/day, and finally 3 months after returning to the baseline dose.
Results
Systolic blood pressure and pulse rate increased from baseline with the increased LT4 dose, and recovered after returning to the baseline dose. Serum thyroid-stimulating hormone (TSH) concentrations decreased at the higher LT4 dose (1.95±2.16 vs 0.47±1.09 mIU/l, $P<0.001$) and recovered after returning to the baseline dose. Serum-free thyroxine levels and HSS-K scores were unchanged during the study period. GDS-K scores improved on the increased dose (9.5±6.6 vs 7.5±4.7, $P=0.029$) and this improvement was maintained after returning to the baseline dose (9.5±6.6 vs 7.4±5.4, $P=0.010$). Higher serum TSH was independently associated with both higher GDS-K and depression risk among those with depressive mood (GDS-K>10) at baseline.
Conclusions
Depressive mood improves with increased LT4 dose, without significant hyperthyroid symptoms or signs, in older adults undergoing thyroid hormone replacement. These findings suggest the potential for varying hypothyroid treatment based on mood status, and that low-dose LT4 treatment may be used as an ancillary treatment in older euthyroid patients with depression.

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AEP914

Thyroid imaging in the management of anti-PD1/PD-L1 induced thyrotoxicosis

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Context
Thyrotoxicosis is the most common endocrine adverse event due totreatment with anti-PD1 and anti-PD-L1. The most common form is destructive thyrotoxicosis whereas persistent, supposedly autoimmune hyperthyroidism (Graves' hyperthyroidism) is rare. The possible role of thyroid imaging (neck ultrasound and scintigraphy) in the differential diagnosis has never evaluated.
Aim
To evaluate the usefulness of neck ultrasound and ^{99}Tc- scintiscan in patients with thyrotoxicosis induced by anti-PD1 and anti-PD-L1 therapy.
Patients and methods We retrospective analyzed clinical, biochemical and imaging data of 15 consecutive patients who were referred to our department for thyrotoxicosis (high levels of FT4 and FT3 and low-to-undetectable level of TSH) ensued during immunotherapy. All patients underwent neck ultrasound and ^{99}Tc-scintiscan at the onset of thyrotoxicosis and periodical tests of thyroid function (15, 30, 45, 60, 90 and 120 days).
Results
All patients were euthyroid before starting immunotherapy. At the onset of thyrotoxicosis median FT4 was 3.05 ng/dl (normal range 0.7–1.7) median FT3 was 6.30 ng/l (normal range 2.7–5.7)At ^{99}Tc- scintiscan 11 patients presented no uptake (Sci-) whereas 4 patients presented diffuse uptake (Sci+). Sci-patients had absent vascularization whereas Sci+ patients had hypervascular pattern at neck ultrasound. No differences in thyroid function tests were observed at the onset of thyrotoxicosis between the two groups. At 30 and 60 days Sci+ patients showed higher levels of FT4 and FT3 compared to Sci- patients ($P<0.005$).All Sci- patients underwent spontaneous remission, whereasall Sci+ patients required treatment with methimazole in order to control thyrotoxicosis. Among Sci- patients, a lower (< 20 ml) thyroid volume was associated with a faster remission. TSH-receptor antibodies, measured as TBI,were negative throughout the follow-up in all patients.
Conclusions
While Sci- patients showed a self limited course of thyrotoxicosis with a remission time inversely related to thyroid volume,Sci+ patients required treatment with methimazole in order to control thyrotoxicosis induced by PD1 and PD-L1 therapy.

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AEP915

Follicular fluid progesterone in thyroid autoantibodies positive women and assisted reproductive technology outcome

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Objective
Progesterone (P4) is essential for successful embryo implantation and preventing miscarriage. The strong connection between thyroid autoimmunity (TAI) and infertility is highlighted in literature. Follicular fluid (FF) is important for the oocyte maturation. The aim of the study was to assess the influence of FF P4 in TAI positive women on assisted reproductive technology (ART) outcome.
Methods
The study included 52 women undergoing ART. Before the initiation of protocol for the controlled ovarian stimulation,thyrotropin (TSH), free triiodothyronine (fT_3), free thyroxine (fT_4), thyroid peroxidase antibodies (TPOAbs) and thyroglobulin antibodies (TgAbs)levels were measured in serum, while TSH, fT_4, TPOAbs, TgAbsand P4 levels were measured in FF on the day of oocyte retrieval. Depending of serum TPOAbs and/or TgAbslevels patients were divided into TAI positive group included 26 patients and 26 age and body mass index matched TAI negative controls.
Results
TAI positive women had less chance to achieve pregnancy ($P=0.004$, OR=0.036, 95% CI 0.004–0.347). However, no statistically significant difference of mean P4 FF level between women with 21 724.2±12 157.3 ng/ml, and without TAI 20 676.6±11 764.9 ng/ml was found ($P=0.754$), and no statistically significant correlation was shown between FF P4 and serum and FF TPOAbs and TgAbs in groups. No statistically significant difference was found between FF P4 and the ART outcome, pregnancy per ET cycle in individual TAI positive and TAI negative groups, although, higher values of FF P4 were observed in subjects with pregnancy per ET cycle with borderline statistical significance ($P=0.060$). It was shown that FF P4 is a significant predictor of ART outcome [log FF P4 $P=0.011$, OR=56.276 (95% Cl 2.542–1245.660)].
Conclusion
To the best of our knowledge, this is the first time to demonstrate the presence of P4 in FF of TAI positive women undergoing ART, and to estimate its impact on ART outcome. FF P4 was shown to be a significant predictor of ART outcome, for both women with and without TAI. Further studies are needed to estimate possible FF P4 threshold affecting ART outcome.

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AEP916

Subclinical hypothyroidism and non-alcoholic fatty liver disease: A systematic review and meta-analysis

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Introduction
Hypothyroidism has been reported as an important factor in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) but studies about the relation between subclinical hypothyroidism and NAFLD have shown contradictory findings. The aim of this study was to conduct a systematic review and meta-analysis exploring the association between subclinical hypothyroidism and NAFLD.
Methods
MEDLINE, EMBASE, Cochrane Library and sources for grey literature (GreyNet international, Google Scholar, Web of Science) were searched from inception to December 2019. The results were supplemented by a manual search of the bibliographies of the articles. The Newcastle Ottawa Scale was used to evaluate the quality of included studies.
ORs were considered as the effect measure with 95% confidence interval and two sided *P* values was calculated for totals and each study. Sensitivity analysis was implemented by excluding studies with low score of quality. Heterogeneity was assessed using χ^2 test and I^2 statistic. Publication bias was evaluated by funnel plot. Review Manager software v.5.3 was used and $P<0.05$ was considered statistically significant.
Results
11 studies were included in the meta-analysis with 41.553 participants (table 1). There was association between subclinical hypothyroidism and NAFLD (OR: 1.27; CI 95%: 1.01–1.60; I^2: 79%; $P=0.04$) (Figure 1). After excluding one study with low quality, subclinical hypothyroidism was significantly correlated with NAFLD (OR: 1.28; CI 95%: 1.01–1.62; I^2: 81%; $P=0.04$). Funnel plot did not show indication of publication bias.

Table 1 Summary of the characteristics of included studies.

Author, year	Country	Study design	Number of participants	Age (years)	Quality
Bano, 2016	Netherlands	Cohort	9.419	64.7	High
Chung, 2012	Korea	Cross-sectional	4.648	48.6±11.8	High
Correa-Morales, 2014	Mexico	Case-control	145	--	Low
Eshraghian, 2013	Iran	Cross-sectional	832	48.2±12.8	Moderate
Lee,2015	Korea	Cohort	18.544	37.8±5.7	High
Lee, 2018	Korea	Cross-sectional	3.452	44.8 (44.5–45.1)	High
Ludwing, 2015	Germany	Cross-sectional	1276	40.7±12.7	High
Parikh, 2015	US	Case-control	800	44.3±3.2	High
Posada-Romero, 2014	Mexico	Cross-sectional	753	51.9	Moderate
Wang, 2014	China	Cross-sectional	806	56.99	Moderate
Xu, 2012	China	Case-control	654	–	High

Conclusion
Our meta-analysis demonstrated that subclinical hypothyroidism increases the risk of NAFLD. The treatment of subclinical hypothyroidism in patients with NAFLD might improve the progress or the occurrence of the hepatic disease and this potential benefit should be further explored by well-designed clinical studies.

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AEP917

Total thyroidectomy for amiodarone-induced thyrotoxicosis: Identification of the surgical candidates and preparation to surgery

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Background
Amiodarone-induced thyrotoxicosis (AIT) is a challenging disease associated with increased morbidity and mortality. The European Thyroid Association guidelines define the role for total thyroidectomy in the management of AIT. However, these recommendations were based on small series, which often lead to heterogeneous results and, importantly, did not identify patients who may benefit from surgery.
Materials and methods
Observational longitudinal cohort study involving 207 AIT patients followed at University of Pisa over a 27-year span. Fifty-one patients received total thyroidectomy and 156 received optimal medical therapy, as defined by the most recent guidelines. Indications to surgery were revised, and surgical candidates were clustered according to the degree of urgency, thus leading to the identification of four surgical groups. Data at diagnosis of AIT and during the course of the disease were recorded. Death and its causes were assessed by telephone interview. Intergroup comparisons were performed between surgical and medical patients, and intragroup comparisons were performed according to the four identified surgical groups. Survival was estimated using the Kaplan-Meier method.
Results
Ten-years overall mortality rate and 5-years cardiovascular-specific mortality rate were lower in the surgical rather than in the medical therapy group ($P=0.04$ and $P=0.01$, respectively). This result was due to the subset of patients affected by moderate-to-severe systolic dysfunction, whereas no differences were reported for patients with normal or mildly-reduced systolic function. Compared to low-risk patients who underwent total thyroidectomy in the elective setting, high-risk patients submitted urgently to surgery due to a worsening of the underlying cardiac conditions were operated more rapidly ($P=0.018$), with a lower left ventricular ejection fraction ($P<.0001$)and with higher thyroid hormone concentrations ($P=0.0002$ and $P=0.013$ for FT4 and FT3), but without any difference in the survival rates ($P=0.486$). At Cox multivariate analysis presurgical thyroid hormone concentrations were not significant predictors of mortality.
Conclusions
Total thyroidectomy should be considered for AIT patients with moderate-to-severe systolic dysfunction, since it is associated with improved survival compared to optimal medical therapy. Patients affected by severe underlying cardiac disease should undergo surgery urgently, avoiding any possible delay aimed at a preliminary restoration of euthyroidism.

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AEP918

PEG precipitation of TSH in subclinical hypothyroidism. A study of 398 samples in real-world setting

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Background
Hypothyroidism is defined as an elevated TSH (thyroid-stimulating hormone) and/or decreased free thyroxine (FT4) levels. Levothyroxine is now one of the most widely prescribed medications. However, treatment indications are controversial in subclinical hypothyroidism, defined as high TSH with normal T4 levels.
Methods
We performed a cross-sectional study reviewing the blood samples received in our Laboratory for TSH determination during the period of 10th Jun 2019–21st Oct 2019. We did not search for access to medical background or any private information regarding the patients whose samples were analysed. Any TSH above the upper limit of normal for our laboratory (4.94 mU/l for adult patients, CMIA, Abbott Architect) and up to 20 mU/l was included to the study group. Among samples with TSH above 20 mU/l, we only included those with normal FT4 or T4 level determined from the same sample. The selected samples were treated with Polyethylene glycol (PEG) in the same manner as for high prolactin levels. We calculated the TSH recovery level (monomeric TSH) as a percentage of the initial TSH level.

For statistical analysis, we used IBM SPSS v.21 and MaxStat v.3.6. We applied non-parametric tests and defined $P<0.5$ as significant.
Results
Of 12 703 samples, 430 (3.4%) met the inclusion criteria. Of these, 398 had available serum for precipitation with PEG. Patients with initial TSH < 15 mU/l were younger than those with TSH 15 mU/l or above ($P=0.03$). The group with recovered TSH percentage of up to 24% ($n=106$) had a lower initial TSH value when compared with 25% or higher ($n=292$) ($P=0.01$). Older age (50 and older, $n=200$) was associated with a higher level of monomeric TSH ($P=0.003$). The initial TSH values of 7.77 mU/l or above had tendency towards higher value of monomeric TSH ($P=0.066$).
Conclusions
Our results suggest there could be a potential role for monomeric TSH determination prior to treatment initiation for subclinical hypothyroidism, mainly in young patients. The main strong point of our study is its real-world setting. The limitations are that we did not take into account the patients' background and treatment; we also did not have a possibility to use gel filtration chromatography which is considered a gold standard for monomeric TSH determination. At the next stage, we are planning to compare these results with a group of patients who have normal TSH values.

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AEP919

The effects of naringenin on NRF2 and antioxidant enzymes expressions in the thyroids of the old-aged Wistar rats

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Citrus flavanone naringenin (NAR) is a potent antioxidant with ability to change pituitary-thyroid function. NAR increases concentration of thyroid-stimulating hormone (TSH) in serum by increasing Sirtuin1 expression in the pituitary thyrotrophs and improves thyroid hormonogenesis capacity in old-aged rats. Thyroid hormone production is followed by generation of large quantities of reactive oxygen species (ROS) which are essential for iodine organification. A master regulator of redox status, NRF2 protein, together with antioxidant enzymes (AOE), is responsible for maintenance of redox/antioxidant balance in the cell. Considering that NRF2 expression can be affected by NAR, besides TSH, the study aim is to analyze gene and protein expressions of NRF2 and AOE in the thyroids of 24-month-old male Wistar rats. NAR was suspended in sunflower oil (vehicle) and administrated directly to the oral cavity, at a dose of 15 mg/kg b.m., during 4 weeks. Control group received vehicle only. We performed qPCR and immunoblot analyses for gene and protein expressions, respectively. Obtained results showed that NAR treatment lowered ($P<0.05$) mRNA levels of Nrf2, superoxide dismutase 1 and 2 (Sod1, Sod2) and catalase (Cat) for 42%, 32%, 45% and 35%, respectively, while it only increased ($P<0.05$) expression of glutathione peroxidase (Gpx) for 54%, all in comparison with the controls. Gene expression of glutathione reductase (Gr) remained unchanged. Also, NAR up-regulated ($P<0.05$) protein expression of NRF2 and SOD2 for 58% and 50%, respectively, and down-regulated ($P<0.05$) SOD1 expression for 48%, all when compared to the adequate control values. CAT, GR and GPx protein expressions didn't change after NAR treatment. It can be concluded that NAR changes gene and protein expression of NRF2 in old-aged rat model. Down-regulation in Nrf2 gene expression, and some AOE, is in line with previously observed TSH stimulation after NAR. Antioxidant protection in thyroid needs to be lowered in order to ensure sufficient ROS for adequate thyroid hormones production. However, due to NAR prooxidant properties, redox status in thyroid upon its application was changed, inducing accumulation of NRF2 protein in the thyrocytes. This led to increment of Gpx gene and SOD2 protein expression, helping in maintenance of fundamental antioxidant protection and disposal of excessive ROS in the thyroid gland of old-aged rats.

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AEP920

Retrospective analysis of low risk thyroid cancers. Total thyroidectomy or lobectomy is the optimal approach for follow up?

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Background
Differentiated thyroid cancer (DTC) <1 cm without risk factors require only lobectomy, and there is no need for radioiodine remnant ablation (RRA). The approach for surgery and RRA after surgery is less clearly defined for tumours measuring 1–4 cm.
Objectives
We aimed to evaluate the surgical approaches of DTC in stages pT1–2 in a moderate iodine deficient area. We compared our data to the current European Thyroid Association (ETA,2006) and American Thyroid Association (ATA,2015) clinical practice guidelines.
Methods
Data of 111 DTC patients treated between 2013–2018 at Flór Ferenc Hospital, Kistarcsa were retrospectively analyzed. The therapeutical response could be evaluated in 96 DTC patients.
Results
81 patients were classified with DTC in stages pT1–2. 64 patients were found in stages pT1, 17 patients were detected in stages pT2. The histological distribution of DTC was 65/81 (80.2%) papillary thyroid cancer (PTC) and 16/81 (19.8%) follicular thyroid cancer (FTC). Lymph node metastases were present in 21.5% of PTC and 0% of FTC. No distant metastases were detected. 25% of pT1 DTC was multifocal (9% limited to one lobe, 16% involved both lobes/isthmus), and 11.7% of pT2 DTC was multifocal (5.8% limited to one lobe, 5.8% involved both lobes). Thus pT1–2 multifocal DTC located in both lobes/isthmus were found in 11 patients (13.5%), all PTC, whereby 4/37 (10.8%) were in stage pT1a, 5/27 (18.5%) were in stage pT1b, 2/17 (11.8%) were in stage pT2. All of them underwent total thyreoidectomy, and in 10 of 11 were done postsurgical RRA. The tumour size in the contralateral lobe was <5 mm in 5 cases, was >5 mm in 3 cases (mean 9.6 mm) and there were no exact data in 3 cases.
Conclusions
In 13.5% of pT1–2 patients (11/81) the tumour involved both lobes, which changes the staging of the disease. The size of the tumour in the contralateral lobe is small in most cases (mean 1.4 mm), this fact makes almost impossible to detect and follow up them by ultrasound. Therefore we suggest total thyreoidectomy in moderate or low iodine supplied areas in T1b–T2 cases to improve the risk stratification, to determine the necessity of RRA and the long-term follow up, which are almost impossible if only lobectomy is being done.

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AEP921

Early diagnosis of medullary thyroid cancer in case of low serum calcitonin: Role of calcitonin measurement in fine-needle aspiration washout fluid

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Background
Screening serum calcitonin (sCT) measurement in patients with thyroid nodules is still debated. Moreover, sCt cutoffs for medullary thyroid carcinoma (MTC) are not univocally defined. Also, sensitivity of cytology by fine needle aspiration biopsy (FNAb) has been demonstrated to detect approximately half of MTCs. Ct measurement in fine-needle aspiration washout fluid (Ct-FNAb) has high sensitivity and specificity and is helpful in case of non-diagnostic cytology[1]. Recently, a series oflow sCt MTC has been collected[2].
Aim
The objectives of this retrospective observational study were to define Ct-FNAb levels in subjects with low sCt (below cutoffs diagnostic for MTC) and to evaluate their clinical, ultrasonographic (US), cytological and histological characteristics.

Methods
We selected subjects with sCt above local normal ranges but below one of the diagnostic cutoff proposed for MTC (26 pg/ml in females and 68 pg/ml in males), subjected to FNAb with Ct-FNAb measurement and then thyroidectomized.
Results
Surprisingly, 50% (8/16) had MTC at histology, 19% cellular C hyperplasia (CCH) and only 31% neither MTC nor CCH. Ct-FNAb was significantly higher in MTC compared to both no MTC no CCH (2001 vs 25.32±55.72 pg/ml; *P=0.013*) and to CCH (2001 vs 195.56±286.09 pg/ml; *P=0.008*). Even if below the diagnostic cutoff, also sCt was higher in MTC compared to no CCH and no MTC group (19±7 vs 9±4 pg/ml; *P=0.019*) but was not able to discriminate MTC from CCH. US failed to identify suspicious nodules, since MTC differed only for being solid and not haloed. At cytology nearly 90% of MTC lesions were non-diagnostic or, mainly, indeterminate. At histology, 7/8 were low risk micro MTCs.
Conclusion
HighCt-FNAb despite sCt only slightly elevated suggests: i) early detection of MTC before the onset of high secretion of Ct, ii) a peculiar variant of MTC, able to produce Ct but not to secrete it in bloodstream because of intracellular secretory pathway alteration, iii) possible methodological interferences in the dosage of sCt. In conclusion, this study demonstrates the importance of Ct-FNAb to discover early stages of MTC with sCt below diagnostic cutoffs.
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AEP922

Impact ofhypothyroidism on early preneoplastic changes at the transcriptomic level in mammalian cells

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Introduction
Studies suggest that disturbed thyroid hormones (TH) homeostasis may lead to increased cancer risk. However, the exact role of TH in cancerogenesis is unknown. We have previously identified 15 genes linked with TH signaling in 7 cancer types and 10.967 cancer patients. Here, we investigated the influence of hypothyroidism on the expression of these 15 genes in rat tissues/organs from which the previously identified, TH-related cancer types originate.
Material and methods
Female Wistar-Kyoto rats were divided into 3 groups: i) treated with methimazole (MMI) (17 mg/kg daily for 8 weeks); ii)thyroidectomized;iii) control rats. $n=3$ rats per group. Gene expression was analyzed (qPCR) in: mammary glands, renal cortex, lungs, thyroid gland, endometrium, liver, ovary, and colon epithelium. Statistical analysis: Student's unpaired t-test, *P*-values <0.05 were considered significantly different. PanCancer analysis of co-expression of genes encoding mesenchymal stem cells (MSC) markers and genes linked to TH signaling was performed using publically available TCGA data from 10.967 cancer patients. The study was approved by the local ethics committee (Second Warsaw Local Ethics Committee for Animal Experimentation) no. *WAW2/022/2018.*
Results
The induction of hypothyroidism in rats was confirmed by serum evaluation of T4 (avg. 0.60 µg/dl) and TSH (avg. 20.23 ng/ml). In mammary and thyroid glands of MMI treated rats, strong induction of analyzed genes expression was observed, including *ARNT, THRA, THRB, SLC16A2, SLC2A1, CTNNB1, NCOA1, HDAC1, CMYC, HIF1A* upregulated in both tissues, and *VIM, CDH1 and TPO*upregulated only in thyroid glands. In the residual MMI-treated tissue types the only significant expression changes were: *HDAC1*downregulation in renal cortex and lungs, *DIO2* downregulation in endometrium, and *THRA* upregulation in colon epithelium. Expression profile in mammary glands ofthyroidectomized rats did not confirm induction of gene expression observed in MMI treated rats. Results of PanCancer TCGA data analysis revealed associations between expressions of genes linked with TH signaling and MSC functioning, including THY1/RCAN2 and ENG/RCAN2 which occurred in 11 cancer types.
Discussion
The study suggests that observed expression changes in mammary and thyroid glands are caused not only by hypothyroidism but also by MMI influence on these tissues. Elucidation of the observed expression changes requires further research. Since MMI, apart from TPO, can interact with other peroxidases like MPO, EPO and LPO,this interaction may lead to decreased selectivity of MMI inhibition and cause broader impact on gene expression.
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AEP923

Adverse effects of tyrosine kinase inhibitors in advanced thyroid carcinoma – a summary of 10-year experience

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Introduction
To date, only four tyrosine kinase inhibitors (TKIs) have demonstrated beneficial effect on progression free survival in advanced medullary thyroid cancer (MTC; vandetanib and cabozantinib) andradioiodine-refractory differentiated thyroid cancer (RR-DTC; sorafenib and lenvatinib). However, there is still lack of unequivocal proofs of their significant impact on overall survival. Therefore, treatment-related side effects and their potential impact on quality of life has been recently widely discussed.
Aim
We conducted a retrospective analysis to evaluate TKIs toxicity in advanced thyroid cancer. The comparison of particular drugs was not aimed.
Material and methods
The study group involved 72 patients at mean age at treatment start of 51 ± 14 years. RR-DTC was diagnosed in 32 patients, whereas MTC in 40 subjects. All side effects were evaluated according to CTCAE (*Common Terminology Criteria for Adverse Events*), V 4.03. The median treatment time was 20.6 months (range: 0.5 months–142.8 months).
Results
In total, 74 treatment courses were assessed: 27 with lenvatinib, 9 with sorafenib, 22 with vandetanib, 9 with cabozantinib, 4 with motesanib, and 3 with axitinib. Treatment-related side effects were present in 97.3% courses. The most common were skin reactions – 68.9% courses, diarrhea – 67.6% courses, hypertension – 59.5% courses, weight loss – 56.8% courses, mucositis – 48.6% courses, abdominal pain– 29.7% courses, fatigue – 29.7% courses, and nausea in 18.9% courses. Skin changes were more frequent in MTC than in RR-DTC patients ($P=0.0128$). Similarly, fatigue was reported more commonly by MTC patients than by RR-DTC patients ($P=0.0387$). Fatigue also occurred more frequently in patients ≥55 years old at treatment onset comparing to younger ones <55 years. This difference was statistically significant ($P=0.0108$). No other significant differences in the frequency of the most common TKI-related side effects were noticed regrading tumor histopathology, age of treatment start, sex, and comorbidities. Due to poor tolerability drug interruption was necessary in 70.3% treatment courses, dose reduction in 62.2% courses, whereas permanent drug withdrawal was required in 25.7% courses.
Conclusions
TKI-related side effects were present in nearly all patients treated due to advanced thyroid cancer. Early diagnosis of adverse effects as well as a supportive management and dose modifications, if necessary, allowed avoiding serious complications and making possible to keep the patient on treatment as long as it was beneficial.
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AEP924

Octreotide and pasireotide effects on medullary thyroid carcinoma (MTC) cells growth, migration and invasion

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Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor of the parafollicular thyroid C cells. Although somatostatin (SS) receptors (SSTs) are expressed by MTCs, treatment with octreotide, specific for SST2, has shown poor efficacy in reducing MTC proliferation, whereas pasireotide, a multi-receptor SS analogue with preferential binding to SST5, has recently demonstrated antiproliferative effects in persistent postoperative MTCs. *In vitro* data in human MTC cell line TT revealed differential responsiveness to antiproliferative and antisecretory effects of SST2 or SST5-selective agonists. Aim of this study was to test the effects of octreotide and pasireotide on MTC cells proliferation, cell cycle proteins expression, MAPK activation, apoptosis, calcitonin secretion, migration and invasion in TT cell line as well as in primary cultured cells obtained from sporadic or hereditary MTCs. Our results showed that both octreotide and pasireotide reduced TT cell proliferation (–41.7±13.8%, $P<0.001$ vs basal, and –31.3±26%, $P<0.05$ vs basal, respectively), with concomitant inhibition of ERK phosphorylation and cyclin D1 expression. This cytostatic effect was accompanied by a proapoptotic action, with an increase of caspase 3/7 activity of 1.4-fold with octreotide and 1.5-fold with pasireotide (both $P<0.001$ vs basal). Moreover, both octreotide and pasireotide inhibited cell migration (-50.9±11.3%, $P<0.01$ vs basal, and –40.5±17%, $P<0.05$ vs basal, respectively, at 10^{-8} M) and invasion (-61.3±35.1%, $P<0.05$ vs basal, and –49.7±18%, $P<0.01$ vs basal, respectively, at 10^{-8} M). No effect was observed on calcitonin secretion after octreotide or pasireotide incubation. In primary cultured cells from MTC, octreotide and pasireotide were effective in reducing cyclin D1 expression in 1 out of 3 tumors, all expressing SST2 and SST5 at similar levels. Octreotide strongly reduced cell migration in 2 tumors tested, regardless of antiproliferative and antisecretory effects and RET mutational status. In conclusion, our data demonstrated a similar efficacy of octreotide and pasireotide in reducing cell growth and invasiveness in TT cells. In contrast,they exerted variable effects in MTC primary cultured cells, independently from the expression of SST2 and SST5, suggesting the need for new biomarkers useful to stratify patients for therapeutic response to SSAs.

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Basal and stimulated calcitonin: Different experience on liaison and cobas assays

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Introduction
The determination of basal and stimulated calcitonin (CT) is very important for the precocious diagnosis of medullary thyroid carcinoma (MTC) and for its dynamic follow-up. Unfortunately, monitoring is difficult when using assays with different detection systems. Our objective was to identify the correction factor between the reagents for CT measurement on the LiaisonXL and Cobase 601 assays (immunochemiluminescence, respectively electro-immunochemiluminescence).
Materials and methods
The measurement rangesare 1–2000 pg/ml for LiaisonXL and 0.5–2000 pg/ml for Cobase 601. All samples above the measuring range were diluted. We selected a group of 89 patients, 28 men and 61 women, with baseline CT or calcium-stimulated CT samples dosed on Cobas, with values between 0.5–2812 pg/ml. The samples were aliquoted and stored at –20ºC, and subsequently analysed on Liaison. The agreement was obtained according to ethical norms through informed consent.
Results
After applying various statistical tests, we found a strong Spearman correlation coefficient between the two assays, of 0.992. There is a segmented linear correlation between the two assays. The general linear regression equation is: $1.108 \times +19.337$ ($P<0.05$), but for higher accuracy we identified the segmented regression equations on two disjoint intervals. The increase of the bias was observed at high CT values: for values between 200 400 pg/ml on Cobas, the linear regression equation becomes $0.807 \times +87.554$ ($P<0.05$), and for values between 400–2812 pg/ml on Cobas, the linear regression equation becomes $0.997 \times +191.094$ ($P<0.05$). We also went on and explored an alternative approach for obtaining a higher accuracy prediction model. Proceeding from the obtained data we developed a software prediction model based on Machine Learning (ML) algorithms, which by design is a prediction model that improves continuously in accuracy of the estimates as more and more data becomes available. In addition, empirical tests have shown that the ML prediction model is superior to the statistical method.
Conclusions
For the first time in literature, we identified the correction factors between Liaison and Cobas assays for CT determination. For the dynamic monitoring of a patient with MTC it is very important to quantify CT with the same method of analysis, and to apply correction factors when using different assays. The results may be influenced by the the fact that the analysys was made on stored samples. Continuing the study on a larger number of fresh samples will ensure increasing accuracy of the correction factors.
Keywords: calcitonin, liaison, cobas, correction factor.
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AEP926

The value of contrast-enhanced 18F-FDG PET/CT for indication of loco-regional surgery in radioiodine-refractory differentiated thyroid cancer

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Aim/Introduction
Contrast-enhanced ^{18}F-FDG PET/CT is an effective diagnostic procedure enabling a precise localization of remnants or recurrences in patients with radioiodine-negative differentiated thyroid carcinomas (DTCs). The detection of this lesions allows to cure patients without detectable distant metastases using a loco-regional surgical treatment. The aim of this study was to assess the influence of ^{18}F-FDG PET/CT on indication of this type of treatment.
Materials and methods
A total of 194 patients (pts) with suspicion of recurrent DTC and negative 131I scans in the period 2008–2019 underwent contrast-enhanced 18F-FDG PET/CT. Examination was performed in 32 patients (pts.) due to suspicious sonography or high-risk disease despite the low TSH-stimulated thyroglobulin (TSH-Tg<2µg/l), in 58 pts. TSH-Tg was 2<10µg/l, in 92 pts TSH-Tg>10µg/l and in 14 pts. due to persistent elevation or increasing level of anti-Tg. Only the first 18F-FDG PET/CT examinations were evaluated, all subsequent examinations of the same patient were not included in this study.
Results
Contrast-enhanced 18F-FDG PET/CT detected remnants or recurrences – usually lymph node (LN) involvement treatable with loco-regional surgery in 38 of 194 pts. In the subgroup with TSH-Tg 0<2µg/l and suspicious sonography or high-risk disease surgery was performed: 5 pts (16%) LN metastases, 2 pts. benign (parathyroid adenoma and Schwannoma) and 2 pts. malignant (spinocellular and renal carcinoma) tumors. Subgroup – TSH-Tg 2<10µg/l: 8 (14%) pts. LN metastases. Subgroup – TSH-Tg>10µg/l: 23 (25%) pts. LN metastasesor remnants (incidentally 2 another malignancies were detected using PET– lung and colorectal carcinoma) Subgroup with anti-TG pathology: 5 (36%) LN metastases.
Conclusion
Contrast-enhanced 18F-FDG PET/CT is an efficient diagnostic tool for indicating patients with radioiodine-negative DTCs to loco-regional surgery. The detection rate of treatable recurrences or remnants significantly increases with increase of TSH-Tg. Nevertheless, it is not possible to set the lower TSH-Tg limit for 18F-FDG PET/CT indication. Surprisingly, a high portion of the pathological findings also show pts. with persistent elevation or increase of anti-Tg. Incidental detections of another types of malignancies is also appreciable.

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AEP927

Association between multifocality and one-year post-surgery response to treatment in papillary thyroid cancer

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Introduction
American Thyroid Association (ATA) guidelines suggest considering hemithyroidectomy in patients with unifocal well-differentiated thyroid tumours,smaller than 4 cm, withoutpreoperative evidence of extrathyroidal extension (ETE) nor lymph node metastases. Although multifocal microcarcinomas are considered to increase the risk of structural disease recurrence from 1%–2% to 4%–6% compared to unifocal microcarcinomas, the ATA guidelines do not suggest different risk stratification for multifocal andunifocal tumours; with the exception of BRAF V600E mutated tumours with ETE, such tumours are low risk when they are unifocal and moderate risk when they are multifocal. Our objective was to evaluate whether multifocality influences response to treatment one year after papillary thyroid cancer (PTC) surgery.
Material and methods
We retrospectively collected every histologically confirmed PTC (non-aggressive variants),larger than 2 mm, operated at our centre between 2001 and 2018. Using the Dynamic Risk Stratification system,we compared responses to therapy at one year of follow-up (1YFU) between multifocal tumours (MFPTC) and unifocal tumours (UFPTC). Using chi square test, we evaluateda possible association between MFPTCand higher risk for incomplete remission (non-excellent: biochemical incomplete, structural incomplete or indeterminate). We also stratified our sample by different variables: biggest focus size, presence of BRAF V600E mutation, treatment with I131 (RAI) and evidence of histological ETE.
Results
We studied 498 patients: 202 MFPTC and 296 UFPTC. Among MFPTC, 149 (73.8%) had an excellent response at 1YFU. Among UFPTC, 264 (89.2%) had an excellent response at 1YFU ($P<0.0001$; RR: 2.94). Higher risk for incomplete response to treatment in MFPTC was maintained when stratified by size, including those larger than 10 mm ($P<0.0001$; RR: 5.49) or 20 mm ($P<0.0001$; RR: 5.39);presence of ETE (*n*: 121, $P=0.02$; RR: 2.47); or including only PTC treated with radioiodine after surgery (*n*: 422; $P<0.0001$; RR: 3.29). A non-significant tendency to more frequent non-excellent response in MFPTC was observed when stratified by detection of the BRAFV600E mutation, with $P=0.06$ in wild type (*n*: 116) and $P=0.13$ in mutated PTC (*n*: 115).
Conclusion
MFPTC are associated with a non-excellent dynamic stratification risk at 1YFU compared with UFPTC, regardless of the size of their largest focus, the finding of ETE,or treatment with RAI. Therefore, we suggest multifocality shouldbe considered by clinicians for decision-making regarding follow-up of PTC patients. Given that total thyroidectomy allows clinicians to assess multifocality, we suggest this procedure for consideration as the routine surgery rather than lobectomy in PTC patients.

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AEP928

Usefulness of tissular heterogeneity analysis measured by elastography in the characterization of tyroid nodules

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Objectives
To assess whether the degree of heterogeneity of thyroid nodules defined by their elastographic characteristics is related to the cytological diagnosis and ultrasound classification of risk of malignancy.
Material and methods
Observational, prospective study. 101 thyroid nodules were analysed by quantitative elastographic analysis (shear-wave), measuring the stiffness of the lesion by global elastography and its standard deviation (s.d.) as an index of the stiffness heterogeneity. US-guided FNA was performed and cytological analysis was confirmed by experienced pathologist, based on the Bethesda system 2017 for reporting thyroid cytopathology.
Results
101 nodules, with an average volume of 5.02±7.01cc, average elasticity of 41.82±28.64 kPa and an average s.d. 19.81±13.61 kPa. The ultrasound characterization of malignancy risk was based on the ACR TI-RADS system 2017, obtaining 19.8% of the nodules as TR2, 26.7% as TR3, 38.6% as TR4 and 14.9% as TR5. After the cytological study 3% of lesions were characterized as non-diagnostic (Bethesda I), 80.2% as benign (BII), 1% as atypia of undetermined significance or follicular lesions of undetermined significance (BIII), 3% as follicular neoplasms or suspicious for a follicular neoplasms (BIV), 3% as suspicious for malignancy (BV) and 9.9% as malignant (BVI). Both higher mean elastographic values and greater heterogeneity of nodules (higher s.d.) were significantly correlated with the ultrasound risk of malignancy and cytological malignancy, with areas under the curve (AUC) in ROC curves of 0.83 and 0.8, respectively, and a NPV of 0.95.
Conclusions
The stiffer nodules and with greater tissue heterogeneity present a greater potential for malignancy, so that analysis of the absolute elastographic value and its intranodular variability can contribute to the differential diagnosis of malignant thyroid nodular pathology. Because of its high NPV, the analysis of tissue stiffness heterogeneity could be a useful tool in the monitoring of benign nodules.

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AEP929

No important salivary gland damage following radioiodine remnant ablation

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Radioiodine (^{131}I, RAI) has traditionally been used in thyroid cancer treatment but its benefitshould be balanced against possible risks. Among them, salivary gland dysfunction has oftenbeen discussed, although the reported data have been inconsistent. While some authors reported functional changes following higher (mostly cumulative) activities, there have been scarce data on the activity of 3.7 GBq (100 mCi) that is most commonly used for RAI remnant ablation (RRA). The aim of our prospective study was to evaluate salivary gland function in 31 thyroidectomised patients (6 men, 25 women; median age, 52 years) before and 4 to 6 months after RRA, using 3.7 GBq ^{131}I-NaI. Salivary gland uptake (reflecting parenchymal integrity) and excretion fraction (reflecting secretory function) werequantitatively assessed with ^{99m}Tc – pertechnetate salivary gland scintigraphy. Pre – and posttreatment values were compared using Wilcoxon signed rank test. No significant difference was observed in parotid (median absolute change, +0.01%; 95% confidence interval, –0.02 to +0.03%) or submandibular (0.00%; –0.02 to +0.02%) glands uptake, as well as in parotid (+0.4%; –4.6 to +6.1%) or submandibular (+3.2%; –1.0 to +8.4%) excretion fraction (absolute values in Table). The calculated power for minimum relevant (relative) difference of 25% and sample size of 31 ranged between 86 and 96% for the individual variables, making our negative results reasonably reliable. They suggest that RRA with the most commonly used ablation activity of 3.7 GBq has no important impact on salivary gland function. Therefore, the concerns about putative salivary gland functional deterioration following RRA are probably unjustified.

Variable	Before RRA	After RRA	*P*
Parotid gland			
Uptake (%)	0.14 (0.10–0.20)	0.13 (0.11–0.20)	0.268
Excretion fraction (%)	49.7 (37.1–60.0)	51.4 (42.8–57.5)	0.899
Submandibular gland			
Uptake (%)	0.15 (0.11–0.18)	0.15 (0.11–0.17)	0.855
Excretion fraction (%)	28.3 (21.9–41.1)	35.7 (22.2–42.4)	0.124

Values are expressed as median (interquartile range), *P* values from Wilcoxon signed rank test.
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AEP930

Graves' disease in assocation with metastatic malignant struma ovarii: A descriptive case

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Introduction
Malignant struma ovarii is a rare disease, for which risk factors and prognostic features are not well-defined. We present a patient with concomitant Graves' disease and metastatic follicular thyroid cancer arising from struma ovarii, and discuss the possible mechanism of this association.
Clinical case
A 43 year old woman undergoing follow-up for Graves' disease (GD) presented with an enlarging left lower abdominal mass. She had a prior history of a left ovarian cystic teratoma with struma ovarii (SO), which had been resected at age 34 years. There was no record of thyrotoxicosis at the time. GD was diagnosed at age 43, when she presented with weight loss, palpitations, and tremours. Free T4 was 48.5 pmol/l [11.8–24.6], TSH < 0.005 mIU/l [0.27–4.2], and TRAb 2.7 IU/l [<1.8] at diagnosis. Thyroid ultrasound (US) revealed heterogenous parenchymal echotexture and increased vascularity. She was started on carbimazole. 4 months later, she reported a sensation of lower abdominal fullness. Pelvic US showed a heterogenous left adnexal mass, measuring 13.8 × 11.6 × 7.1 cm. Left salpingo-oopherectomy followed. Intra-operatively, peritoneal nodules were visualised; histology confirmed intra-ovarian thyroid tissue housing a highly-differentiated follicular thyroid carcinoma, with metastatic peritoneal deposits. Computed tomography of the chest and abdomen did not show any gross evidence of distant metastasis. Completion hysterectomy, right salpingo-oopherectomy, omentectomy, and debulking surgery was performed. Intra-operatively, more metastatic foci were identified on the right fallopian tube and infundibulopelvic ligament, uterovaginal fold, bladder and rectal walls, and peritoneum. A total thyroidectomy followed; histology showed no evidence of intra-thyroidal malignancy. I-131 therapy was administered. The post-therapeutic I-131 whole body scan revealed multiple intra-abdominal foci of uptake, representing remnant disease. At 1 year's follow-up, the patient remains on levothyroxine therapy, with a TSH goal of <0.1 mIU/l. A repeat radioiodine scan is planned. Anti-TG titres have trended downward, and she remains clinically well.
Discussion
To our knowledge, this is the first reported case of metastatic malignant SO in the setting of GD. GD appears to be associated with an increased incidence of differentiated thyroid cancer (DTC); DTC in these situations might behave more aggressively. This association may well apply to the risk of malignant transformation in SO tissue. TSH receptor antibody and local cytokine production might contribute to the pathophysiology.

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AEP931

Evaluation of miRNA-222, –146b, –181b as possible diagnostic markers in patients with papillary thyroid carcinoma

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Introduction
The sensitivity and specificity of biomarkers which have been used in clinical practice for diagnosis of papillary thyroid carcinoma (PTC) are low. It is essential to develop novel diagnostic biomarkers for PTC.
Objective
We aimed to explore the expression levels of miR-222, – 146b, –181b in PTC tissue and plasma samples and to compare with benign thyroid nodules (BTN).
Methods
We collected plasma samples from the patients just before the thyroidectomy due to PTC or BTN. Tissue samples were also collected from the subgroups of these patients. The expression levels (2^-□Ct) of plasma miR-222, –146b, –181b were measured in 48 samples from patients with PTC and 22 from patients with BTN. Expression of the same set of miRNAs in PTC and BTN tissue samples were investigated in subgroups of 19 and 9 patients, respectively.
Results
A significantly higher expression levels of miR-146b were observed in PTC tissue samples (4.433 ± 6.04), compared to BTN (0.151 ± 0.094), (P = 0.001). However, the results of plasma samples indicated that levels of miR-222, –146b, –181b had no significant differences in the PTC patients compared with BTN (P = 0.424, P = 0.641, P = 0.427, respectively).
Conclusion
Many studies are underway to discover minimally invasive method for PTC diagnostics. In our study we analyzed expression levels of miR-146b, –222, –181b and we found that only mir-146b expression levels were significantly higher in PTC than in BTN tissue samples. However, there were no significant differences while comparing expression levels of this set of miRNAs in PTC and BTN plasma samples. Unfortunately, the value of these three miRNAs is still limited in differential diagnosis of PTC and BTN from plasma samples.

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AEP932

Comparative assessment of several ultrasound imaging systems

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The purpose of the study was to evaluate the diagnostic capabilities of systems for assessing ultrasound thyroid imagines. The object of the study was 754 patients with thyroid nodules. Research methods: ultrasound in the framework of image evaluation systems TIRADS, EU-TIRADS, ARC-TI-RADS, BTA, TI-RADS K. For statistical analysis of systems and criteria was performed multidimensional statistical modeling using cluster, factor, discriminant, variance, and ROC analysis. The study found that the systems have different sensitivity and specificity. Data have shown that there are more differences between systems than there are similarities. The reason for this is that there are no uniform rules for the formation of systems. The authors of the systems arbitrarily determined a set of features, their combinations, staging, accounting or not accounting for the size of thyroid nodes. According to the ROC analysis for thyroid cancer, the sensitivity of TIRADS was 91%, specificity-91%, diagnostic efficiency-91%, prognostic value of a positive result-0.92, the likelihood ratio for a positive result-10.6, the likelihood ratio for a negative result-0.03. When detecting thyroid adenomas, TIRADS sensitivity was 62%, specificity-82%, diagnostic efficiency-79%. When detecting goiter, TIRADS sensitivity was 86%, specificity-83%, diagnostic efficiency-79%. ROC analysis found that AUC = 0.972 ± 0.00 484. AUC is an integral measure of diagnostic effectiveness, it can be argued that TIRADS has good predictive capabilities in thyroid cancer, good in goiter, and insufficient effectiveness in adenomas. When comparing the systems, it turned out that the ACR-TI-RADS system, despite the decrease in the number of signs, has the highest prognostic indicators for thyroid cancer (AUC = 0.964) and slightly worse for thyroid adenomas and nodular goiter. The Korean TI-RADS-K system is a test of excellent quality (AUC = 0.959) with good prognostic indicators for various nodular thyroid pathology. In terms of specificity (97%), TI-RADS-K is superior to all other systems. When evaluating EU-TIRADS, it is established that the system is a test of high quality (AUC = 0.826), but has a predictive capability worse than TI-RADS. The BTA system has the lowest prognostic indicators of all systems (AUC = 0.823). With Multidimensional Scaling, TIRADS (coordinates: 0.80 043; 0.58 114) and ACR-TI-RADS (coordinates: 0.58 114; 0.52 5725) were close. The Correlation Analysis of a Two-Way Table confirmed the influence of empirical ranking on the results of system evaluations. Gradations related to thyroid cancer have a large diagnostic weight, and the ranking of benign pathology introduces an element of instability in the system, without significantly affecting the final result-the selection of patients for fine-needle aspiration biopsy.

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AEP933

Thyroid hormone resistance and succesful gestation with unaffected fetus: A case report

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Thyroid hormone resistance (THR) is a rare dominantly inherited syndrome characterized by a reduced response of target tissues to thyroid hormone receptor. In most cases, THR is related to mutations in the thyroid hormone receptor beta gene (THRb). Management may be challenging in cases of gestation. Here we report the case of a pregnant patient with a possible not previously described mutation and negative genotype fetus.
Case report
Thirty-two year old patient asked for consultation for free T4 elevated levels (2.42, normal values: 0.93–1.7 ng/dl) with normal TSH values (3.6, normal values: 0.5–8.9 βUI/ml). Patient was asymptomatic and neither goiter nor thryoid autoinmunity was found. Genetic test detected in heterozygosis one variant of unknown significance in THRβ (c.737T>C (p. L246P). She was asked for family members with possible thyroidopathy and THR was also diagnosed in her father. He exhibits as well the same genetic variant. Patient got pregnant being TSH and free T4 levels 3.98 mUI/ml and 3.03 ng/dl respectively. As fetal DNA obtained by amniotic fluid ruled out that fetus was affected, treatment with PTU was started in order to mantain free T4 levels lower than 20% of the upper limit of normal. Fetal ecography showed normal fetal weight and free T4 levels were in desired range with doses of 200 mg/day PTU. Caesarean section was held 3 days before the estimated day of delivery due to prelabor rupture of membranes. Masculine infant born weighted 2760 grams and APGAR was 9/10/10.

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AEP934

Myasthenia gravis associated with Graves' disease: About three cases

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Introduction
The coexistence of Grave disease [GD] and Myasthenia gravis [MG] may present a diagnostic dilemma especially concerning ocular manifestations. 3–10% of myasthenic patients exhibit GD, while MG is reported in only <1% of patients with thyroid disorder.
Observation
Case 1
A 32-year-old woman, with a medical history of vitiligo, was diagnosed with GD. Immunology revealed positive anti-thyroid peroxidase antibodies [TPOAb] and TSH receptor antibodies [TRAb]. Treatment with Anti-thyroid drugs was soon withdrawn because of severe eruption and the patient received radical treatment (I-131). Two months later, she reconsulted for muscle use increasing throughout the day. The diagnosis of MG was confirmed by a Prostigmine test, and positive Acetylcholine receptors [AChR] antibodies. The treatment with Pyridostigmine was immediately initiated. But, the amplification of myastenic symptoms later led to successive immuneglobulin cures.
Case 2
A 43-year-old man consulted for exophthalmia, diplopia, asymmetric ptosis and blurring of vision. Physical examination demonstrated a goiter, a resting tremor and proximal muscle weakness. Thyroid function test showed high levels of thyroid hormones, TSH<0.05. Both GD with severe ophthalmopathy and MG were suspected. Immunology confirmed the diagnoses, with positive TRAb, TPOAb and AChR antibodies. The patient was started on Thiamazol and Pyridostigmine, with a good evolution.
Case 3
A 41-year-old woman complaining of asthenia by the end of the day, diplopia and difficulty chewing. She reported a medical history of GD treated for 2 years with Benzylthiouracil, then Radioiodine at the age of 28. AChR antibodies and Anti-striated muscle Antibodies were positive confirming MG's diagnosis, with a thymic tumor revealed on chest scan. Therefore, the patient underwent a total thymectomy that in association with cholinesterase inhibitors was fairly efficient.
Conclusion
GD is associated with a number of autoimmune diseases, including myasthenia. Two out of our three patients had ocular myasthenic symptoms. Thyroid disease was found to be more frequent in ocular MG patients (40%) than in generalized MG patients (12%). Accordingly, it is important for every endocrinologist to suspect the association of MG in each GD patient especially on the presence of ptosis, exotropia, muscle weakness increasing with exercise.

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AEP935

Thyroglossal duct cyst papillary thyroid cancer in a 40-year-old female: Case report

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Introduction
The thyroglossal duct develops during thyroid gland formation and usually involutes at 7–10 weeks gestation. Its residue can lead to formation of cysts as well as to develop neoplasms within the mass.
Case report
A 40-year-old woman was admitted to Department of Otolaryngology because of an enlarging midline neck mass for the last few months, without other worrisome symptoms. A neck ultrasound and CT scan showed a cystic lesion with solid components measuring 20 × 18 mm in size, located above the larynx. A Sistrunk procedure was performed. On histological postoperative examination, thyroid papillary microcarcinoma with microcalcifications in the cyst wall was revealed. The lesion did not infiltrate the capsule and it was completely resected. The patient was referred to Department of Endocrine Oncology for additional testing. Thyroid ultrasound showed 6 × 8 × 9 mm lesion in the left lobe. FNAB was performed and the diagnosis of benign nodule was made (Bethesda class II). As there were no demonstrable cancer or lymph node metastases, the decision of total thyroidectomy has not been made. Levothyroxine therapy has been started with doses adjusted to achieve thyrotropin levels of 0.4 to 1.0 mU/l and further check-up has been recommended. After two years follow-up, there is no progression of thyroid left lobe nodule but in ultrasound imaging an enlarged heterogenous (with calcifications and vascularization) lymph node (32 × 10 mm) next to the left mandible angle has been observed. The patient is currently being diagnosed to confirm or exclude lymph node metastases to decide of total thyroidectomy and neck dissection as well as postoperative radioactive iodine therapy.
Conclusions
Rare prevalence of thyroglossal duct cyst carcinoma, lack of typical features distinguishing benign and malignant lesions before surgery cause the proper diagnosis can be difficult and is usually made postoperatively. The extent of treatment is also not well agreed upon. Therefore, case reports and case series are needed to determine optimal management.

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AEP936

Primary percutaneous coronary intervention induced thyroid storm and acute coronary syndrome: A case report

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Background
Thyroid storm is an extreme disorder that occurs in case of severe thyrotoxicosis. This is a life-threatening condition with mortality rates up to 10–20%. A typical dose of iodinated contrast media (ICM) contains approximately 13.500 µg of free iodide and 15 to 60 g of bound iodine, which represents an acute iodide load of 90 to several hundred thousand times the recommended daily intake of 150 µg. As a result of sudden exposure to high iodide loads, thyroid hormone regulation can be disrupted, leading to hypothyroidism (Wolff-Chaikoff effect) or hyperthyroidism (Jod-Basedow phenomenon), particularly in those with underlying nodular thyroid disease.
Case description
A 37 years old man, presented to the emergency room (ER) with clinical and ECG signs of acute myocardial infarction (AMI). Primary percutaneous coronary intervention with the administration of ICM has been performed. After the intervention, laboratory analyses reviled thyrotoxicosis, and he was given initial thyrosuppressive therapy with cardiac therapy and was discharged from the hospital. One week later, he returned to the hospital with the signs of thyroid storm. His thyroid hormones were high (FT4 260 pmol/l, undetectable TSH) and he scored 45 points on Burch-Wartofsky Point Scale. His therapy was changed into propylthiouracil 4 × 300 mg, Dexamethasone 2 × 4 mg, and Lugol's solution. His condition was further complicated with a spread of skin lesions that looked like vasculitis. Since there has been a great concern that this was propylthiouracil induced vasculitis the drug was replaced with thiamazole. It has been decided that the definitive therapy for the patent condition is surgical ablation. After prolonged hospitalization successful total thyroidectomy was performed after FT4 fall below 30 pmol/l. Pathophysiology examination of thyroid gland reviled colloid nodal goiter, which was not in correlation with the echosonography findings.
Conclusion
We presented an unusual case of thyroid storm in a patient that developed AMI and without a history of thyroid disease prior to cardiac angiography with ICM used. We aimed to raise attention on the routine evaluation of thyroid function in patients with and without previous signs and symptoms of thyrotoxicity and who had an AMI, that undergone coronary angiography. Moreover, this could be an asset as progressively more people with coronary disease will undertake this procedure. If increased thyroid hormones are detected, a patient should be carefully monitored in intensive care units.
Keywords: thyroid storm, iodinated contrast, PCI, acute myocardial infarction, PTU.

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AEP937

Hashimoto's thyroiditis in a patient with IgG4 related disease

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Introduction
Immunoglobulin G4 related disease (IgG4-RD) is an immune-mediated fibro-inflammatory condition and is a widely recognised multi-organ system disease. The prevalence of IgG4-RD is 6/100 000, but it is likely to be underestimated. IgG4-RD is characterised by elevated serum levels of IgG4 and IgG4-positive lymphoplasmacytic infiltrative lesions in the body. Recent reports suggest disease involvement in various organs including thyroid and orbital tissues. Thyroid disease described in IgG4-RD encompasses Hashimoto's thyroiditis, fibrosing variant of Hashimoto's thyroiditis, Reidel's thyroiditis and Graves disease.
Case presentation
A 47-year-old lady was referred to the Endocrine clinic with primary hypothyroidism [TSH 78.2 mIU/l (0.27–4.20), fT4 1.2 pmol/l (12–22) and fT3 < 0.4 pmol/l (3.1–6.8)].There is a family history of thyroid disorder. She had strongly positive TPOAb (>500 IU/ml) and TgAb (>5000 IU/ml), and was diagnosed with Hashimoto's thyroiditis. Thyroxine replacement was started. Initial examination revealed a small diffuse goitre with bilateral periorbital swelling on the upper lids and mild proptosis. A left thyroid nodule was palpable in subsequent visit and USS neck with FNAC was performed. Both thyroid lobes were hypoechoic and lobular in appearance with a 1.1 cm × 0.7 cm hypoechoic nodule in the medial left thyroid. FNAC of the thyroid nodule showed lymphocytic infiltration consistent with Hashimoto's thyroiditis. Serum IgG4 level was markedly elevated (2230 mg/dl; 2.4–121). She was referred to the Rheumatology clinic with suspected IgG4-RD. MRI orbit confirmed bilateral lacrimal gland enlargement. Biopsy of the lacrimal gland showed marked inflammatory cell infiltrates including lymphocytes and plasma cells. Immunostaining revealed increased numbers of IgG4 positive plasma cells among infiltrating lymphocytes. The findings were consistent with IgG4 associated ophthalmic disease. Prednisolone was started following a diagnosis of IgG4-RD.
Discussion
Our patient has Hashimoto's thyroiditis with underlying IgG4-RD. Hashimoto's thyroiditiscan be further subclassified into IgG4-thyroiditis and non-IgG4 thyroiditis. Thyroid nodule FNAC could not confirm the subtype of Hashimoto's thyroiditis in our patient. However, she has significantly elevated TPO-Ab and Tg-Ab and hypoechoic thyroid gland on ultrasonography. These features on a background of IgG4-RD suggest our patient has IgG4-thyroiditis. Bilateral lacrimal gland enlargement is in keeping with IgG4-RD manifestation in the eye which usually causes painless swelling of the lacrimal glands with chronic lid swelling and proptosis. Diagnosis of IgG4-RD can be challenging as it is uncommon and requires a combination of clinical features, serological confirmation and histological evidence with IgG4 immunostaining. The first line of treatment is usually glucocorticoid therapy. Prompt diagnosis and treatment can reduce progression of the disease.
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AEP938

Severe hypothyroidism secondary to Hashimoto's thyroiditis and its implications for surgery

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Background
The prevalence of hypothyroidism is around 1–2% in the UK. Hashimoto's thyroiditis is thought to cause 0.1–2% of overt disease and 10–15% of subclinical hypothyroidism. This case presents a patient with severe hypothyroidism, secondary to Hashimoto's thyroiditis, found incidentally on a surgical admission. The case study discusses the challenges and management of severe hypothyroidism in the need for an acute surgical intervention.
Clinical case
A 72 year-old man was brought into the Emergency Department after a road traffic accident. He was found to have right tibial and fibular shaft fractures, and was incidentally discovered to have sinus bradycardia secondary to profound hypothyroidism. Thyroid function tests done on admission showed a thyroid stimulating hormone (TSH) level of 227 mIU/l (0.27–4.2 mIU/l) and free T4 level of 0.8 pmol/l (12–22 pmol/l). Anti-thyroid peroxidase antibody (anti-TPO) level was >1300 IU/ml (positive if >100 IU/ml), suggestive of Hashimoto's thyroiditis. The patient underwent two surgeries for fixation of fractures, whilst having thyroid hormone replacement. Oral levothyroxine was started and up titrated according to clinical and biochemistry response. Intravenous liothyronine was also used intraoperatively for management of bradycardia and reducing the risk of myxoedema coma.
Discussion and conclusion
Surgery and anaesthesia can precipitate complications associated with hypothyroidism, such as cardiovascular collapse, respiratory failure, and worryingly,myxoedema coma. Altered respiratory physiology and renal clearance of drugs also increase patients' sensitivity to drugs commonly used in anaesthesia. It is recommended to postpone elective surgeries until a euthyroid state can be achieved, through thyroid hormone replacement. Urgent or emergency surgical admissions should be managed with awareness of complications. Mild or moderate hypothyroidism should be managed with hormone replacement therapy and can continue with surgery. NICE Guidelines recommend treatment of hypothyroidism with levothyroxine replacement. Combination therapy with liothyronine should only be used in selective cases and directed by accredited endocrinologists. Although there is a lack of outcome data to guide management of severe hypothyroidism requiring urgent surgical management, studies support, and have shown success in, the use of combination therapy of levothyroxine and liothyronine to reduce risk of severe complications,particularly myxoedema coma. Our case demonstrates an example of an approach to the management of profound hypothyroidism associated with bradycardia and the risk of developing myxoedema coma. Whilst the patient remained bradycardic intraoperatively, he did not suffer from cardiovascular collapse or develop myxoedema coma. He subsequently recovered uneventfully from both surgeries with no serious surgical complications associated with hypothyroidism.
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AEP939

Cardiovascular clinical presentation of inpatients with overt hyperthyroidism – a retrospective study in 250 patients

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Background
The clinical presentation of hyperthyroidism has been studied in the ambulatory caresetting. Our hospital performs a TSH test for all newly admitted patients.
Aim
To describe the clinical presentation of patients with overt hyperthyroidism during hospitalization and to study the association between thyroid hormone levels and the clinical picture.
Methods
A retrospective study of 250 hospitalized patients from an 11-year period (2008–2018) admitted to the internal medicine, geriatrics, or cardiology wards who had a confirmed diagnosis of overt hyperthyroidism.
Results
The mean age was 70±15 years, with a female:male ratio of 1:1. Out of 250 patients, 174 (69%) suffered from previous cardiovascular disease and 111 (44%) presented with a cardiovascular syndrome, including active ischemic heart disease (29, 12%) decompensated congestive heart failure (83, 32%) or new onset atrial fibrillation/flutter (14, 6%). The most common underlying etiology was amiodarone induced thyrotoxicosis (53, 21%), closely followed by overtreatment of previously known hypothyroidism (50, 20%) and toxic multinodular goiter (42, 17%), while Graves' disease was less common (18, 7%). In 51 (20%) an underlying cause could not be determined. No direct correlation was observed between the levels of fT4 and fT3 and any of the symptoms, signs or clinical syndromes; however, in the categorical analysis, elevated fT3 levels, rather than fT4, above the upper limit of normal range (ULN) was associated with cardiovascular presentation. The only symptom that was significantly related to high fT4 values was chest pain ($P<0.001$) while high levels of fT3, in contrast, were associated with palpitations ($P=0.016$), chest pain ($P<0.001$) and cardiovascular syndromes in general ($P=0.007$).
Conclusions
Most hospitalized patients with overt hyperthyroidism had cardiovascular comorbidities, while at the same time presenting with signs of active decompensated heart failure, arrhythmias or coronary artery disease as reasons for hospital admission in ±50% of the patients. Cardiovascular presentation was associated with high levels of fT3 rather than fT4.

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AEP940

Hyaluronan in part mediates IL-1beta-induced inflammation in human thyrocytes by up-regulating TLR-4 and CD44 receptors

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Background
The expression of thyroid-specific genes [thyroglobulin (Tg) and sodium iodide symporter (NIS)] is modulated by several cytokines (IL-1, IFNγ, TGF-ß) and it is down-regulated in Hashimoto's thyroiditis (HT). Also, lymphocytic infiltration and inflammation in HT results in intra-thyroidal accumulation of hyaluronan (HA). During inflammation, HA can be degraded into small fragments, able to up-regulate pro-inflammatory genes by stimulating the toll-like receptors (mostly TLR-4) and CD44, via NF-kB activation. The present study was aimed to evaluate the potential role of small HA fragments, as mediators of TLR-4 and CD44 activation, inIL-1-beta-induced inflammation in human thyrocytes *in vitro*.
Methods
Primary thyrocytes were obtained from patients undergone surgery for benign thyroid nodules. Cultured cells were treated for 24 h with IL-1β (5 ng/ml), with and without TLR-4 and CD44 blocking antibodies, and the hyaluronan binding protein (HABP), which inhibits HA activity. HA concentration was measured by ELISA, while molecular size was assayed by agarose gel electrophoresis. mRNA and related protein levels of TLR4, CD44, interleukin-6 (IL-6), matrix metalloproteinase-13 (MMP-13), thyroglobulin (Tg) and sodium iodide symporter (NIS)were evaluated by real-time PCR, Western Blot and ELISA, respectively. NF-kB activation was also assayed.
Results
IL-1beta induced an increase of HA production and accumulation, that primarily consisted of low molecular weight (LMW) fragments. TLR4 and CD44 levels were higher than controls in thyrocytes treated with IL-1beta. IL-1beta also induced NF-kB up-regulation and increased IL-6 and MMP-13, while reduced Tg and NIS expression. Treatment of thyrocytes exposed to IL-1beta with specific TLR-4 and CD44 blocking antibodies and/or HABP, reduces NF-kB activation and pro-inflammatory mediators production, while partially restore Tg and NIS levels. These findings suggest that IL-1beta exerts inflammatory activity in part via TLR-4 and CD44 by the mediation of small HA fragments derived from HA depolymerization.
Conclusion
In human thyrocytes, IL-1β promotes accumulation of LMW HA fragments anddown-regulate thyroid-specific genes expression via CD44/TLR-4/NF-kB signaling activation. Accumulation of HA pro-inflammatory fragments may play a role in the pathogenesis of thyroid inflammation and damage in autoimmune thyroid disease.

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AEP941

Thyroid hormone levels is not associated with non-alcoholic fatty liver disease in euthyroid subjects

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Backgroud
Recent studies have shown an association between thyroid hormone levels and non-alcoholic fatty liver disease(NAFLD). However, there have been some inconsistencies between studies. Here, we evaluated the relationship between thyroid hormone levels and NAFLDin euthyroid subjects.
Methods
A retrospective analysis of 27.719 euthyroid subjects who participated in comprehensive health examinations was performed. Subjects were grouped according to thyroid stimulating hormone (TSH) and free thyroxine (FT4). We estimated the odds ratios (OR) for NAFLD according to thyroid hormone quartiles using logistic regression models, adjusted for potential confounders.
Results
Of the study patients, 33% ($n=9.217$) had NAFLD. A lower TSH level and higher FT4 level were associated with NAFLD. The proportion of participants with NAFLD decreased across the TSH quartile categories and increased across the FT4 quartile categories. No associations were observed between thyroid hormone and NAFLD after additional adjustment for confounding variables.
Conclusion
Our study demonstrates no significant association between thyroid hormone and NAFLD.

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AEP942

Predictive value of free triiodothyronine within normal range on cardiovascular events in a Chinese cohort with coronary artery disease: Direct effect and mediation effect by TG

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Background and aims
Coronary artery disease (CAD) plays an important role in global mortality worldwide. Risk assessment for patients with CAD through free triiodothyronine (FT3) remains unclear. Therefore, we aimed to investigate the impact of FT3 on the prognosis of patients with CAD.

Methods
A total of 0 patients with CAD and available FT3 data, and without overt thyroid disease were enrolled in this study and grouped by tertiles. The primary outcome was termed cardiovascular events (CVEs), including cardiovascular mortality, non-fatal myocardial infarction and stroke. Association of FT3 with 3-year CVEs was assessed through multivariate Cox regression analysis and mediation analysis.
Results
During median follow-up 2 years, 162 (2%) CVEs occurred. FT3 levels were negatively associated 5824 with incident CVEs (hazard ratio, 0.59; 95%confidence interval, 0.36–0.96). Compared with the low FT3 tertile, the high tertile had significantly lower risk of CVEs (HR, 0.59; 95% CI, 0.38–0.92). Meanwhile, triglyceride mediated the association between FT3 and risk of CVEs (HR, 0.98; 95% CI, 0.969–0.996; $P<0.05$). Moreover, FT3 significantly improved discrimination and reclassification of the Framingham secondary event model and the ABC-CHD model in our cohort. Results remained similar or became stronger in FT3 levels within the normal range.
Conclusion
Lower FT3 levels were associated with an increased risk of CVEs, partly mediated through higher triglyceride, suggesting that FT3 is a potential biomarker for a better risk stratification and perfect management in patients with CAD. Further studies are needed to confirm our findings.

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AEP943

Serum levels of myostatin in patients with hyperthyroidism or euthyroidism

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Objective
Myostatin may negatively regulate skeletal muscle mass. Serum myostatin levels have positive associations with obesity and insulin resistance. Thyroid dysfunction may affect body weight, energy expenditure, and glucose metabolism. We evaluated the serum myostatin levels in different thyroid function statuses.
Subjects and methods
We recruited 30 newly-diagnosed hyperthyroid (HY) patients and treated them with anti-thyroid regimens as clinically indicated. Thirty euthyroid (EU) patients were recruited as controls. We measured laboratory parameters at the baseline and at 6 months, and calculated their changes. Associations between the levels of myostatin and free thyroxine (fT4), thyroid-stimulating hormone (TSH), or log transformation of TSH (logTSH) were analyzed.
Results
There were no significant difference of myostatin levels among the HY and the EU patients, both at baseline (median [Q1, Q3]: 16.25 [11.42, 20.23] vs 17.50 [11.80, 21.56] ng/ml, $P=0.599$) and at 6 months (median [Q1, Q3]: 27.27 [19.11, 32.66] vs 23.20 [16.02, 29.43] ng/ml, $P=0.306$). Serum myostatin levels had no associations with levels of fT4, TSH, or logTSH, both at baseline or 6 months. However, changes of myostatin had positive associations with changes of logTSH ($\beta=2.323$, $P=0.019$). The association between changes of myostain levels and changes of logTSH remained significant after adjustment for sex and age ($\beta=2.505$, $P=0.015$).
Conclusions
Serum myostatin levels of the HY patients were not different with that of the EU patients. In this study, changes of serum myostatin levels had positive associations with changes of logTSH. The real impact of thyroid function statuses on myostatin levels remained to be investigated.

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AEP944

Hypercalcitonemia in a patient with micronodular goiter and adrenal nodular hyperplasia-diagnosis challenge

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Introduction
Hypercalcitoninemia has frequently been reported as a marker for medullary thyroid carcinoma (MCT). Still, several physiologic and pathologic conditions other than MCT have been associated with increased levels of calcitonin, including neuroendocrine tumors that can ectopically secrete calcitonin.
Case report
We present the case of a 78-year old female patient, incidentally diagnosed with multinodular goiter when performing Doppler ultrasound for the evaluation of severe dizziness. In the last 6 months she was admitted in the emergency room several times with paroxysmal symptoms including fronto-occipital headache, severe hypertension, diaphoresis and anxiety. She had normal thyroid function, but high serum calcitonin, carcinoembryonic antigen (CEA) and chromogranin A levels (210.5 pg/ml, 7.36 ng/ml and 159.1 ng/ml, respectively). The thyroid ultrasound revealed a micronodular goiterwith infracentimetric inflammatory lymph nodes (the largest nodule 0.78/0.83/0.9 cm having a spongiform appearance). The abdominal ultrasound showed left adrenal hyperplasia (20/25/25 mm) and an adrenaladenoma (10/10 mm). The plasmatic metanephrines and normetanephrines were in the normal range, but thedexamethasone suppression test was abnormal (6.01 microg/dl). She underwent unilateral adrenalectomy with a favourable outcome in terms of hypertension control. The histopathology report confirmed adrenocortical nodular hyperplasia. Postoperatively, hypercalcitonemia persisted (196.7 pg/ml) and she had total thyroidectomy with central neck lymph node dissection performed with a significant decrease of serum calcitonin level (46.4 ng/ml) accompanied by CEA normalisation (1.99 ng/ml).
Conclusion
Several types of neuroendocrine tumors, including paragangliomas and pheochromocytomas might be associated with increased levels of calcitonin, but the basal calcitonin values in this conditionsusually varies between 10 and 100 pg/ml. Patients with calcitonin levels > 100 pg/ml have a high risk for MCT (90%–100%) and they should be carrefully evaluated although the symptomatology may point out to a different disorder.

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AEP945

MMP-9 1562 C/T polymorphism may be associated with an increased susceptibility to develop micropapillary thyroid cancer but not more advanced tumours

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Background
Matrix metalloproteinase-9 (MMP-9) is an important mediator of invasion and metastasis in neoplasia. The single nucleotide 1562 C/T polymorphism in the promoter region of the MMP-9 genewas shown to increase gene expression and was studied as a susceptibility factor for various cancers.
Aim
We aimed to evaluate the impact of the MMP-9 promoter genotype on the risk of developing papillary thyroid cancer (PTC) and to correlate cancer patient genotype with the pre-surgery serum MMP-9 levels and clinical and pathological features of tumor aggressiveness.
Patients and methods
We evaluated 213 patients referred for thyroidectomy, divided according to pathology into: benign disease (BD) ($n=102$) and PTC ($n=111$). Genomic DNA was isolated from whole blood in all patients and the presence of theMMP-9 1562 C/T polymorphism was evaluated by PCR-RFLP analysis. Pre-surgical serum MMP-9 levels were available in 90 BD and 81 PTC patients. MMP-9 was measured by Elisa (R&D Systems).
Results
Genotype frequencies were in Hardy-Weinberg equilibrium for both patients and controls. T allele was significantly more frequent in PTC patients compared to BD: the combined CT+TT genotype was present in 37 PTC (33.3%) compared to 16 BD patients (15.7%), $\chi^2=8.86$, CI [1.384–5.219], $P=0.0029$. The 1562 C/T genotype did not significantly correlate with presurgical serum MMP-9 levels in either BD or PTC patients; in cancer patients the genotype was not associated with histological subtype, presence of invasion or risk of recurrence. However, the CT+TT genotype was significantly more frequent in tumors smaller than 1 cm compared to larger

tumors ($P=0.016$) and after excluding small intra-thyroidal micropapilllary carcinomas (MPTC) ($N=21$), the association between genotype and BD/PTC diagnosis was lost ($P=0.09$).
Conclusion
The presence of the functional 1562 C/T polymorphism in the promoter region of the MMP-9 gene may indicate susceptibility to develop thyroid cancer. However, the association between the T allele and intrathyroidal clinically non-relevant MPTC may suggest that although this may be a predisposing factor, other genetic/epigenetic events are needed for cancer progression. The 1562 C/T polymorphism might not be clinically useful as a prognostic factor.
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AEP946

Papillary thyroid cancer with biochemical incomplete response: Clinico-pathological characteristics and disease outcome

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Objective
Althoughmost Papillary Thyroid Cancer (PTC) patients with biochemical incomplete response (BIR) to primary therapy have a good clinical outcome, some will develop disease progression. We aim to study baseline characteristics and long-term outcomes of PTC patients with BIR.
Methods
Of 1049 PTC patients treated at 2 tertiary medical centers, 795 (75.8%) had excellent, 91 (8.7%) biochemical incomplete, 139 (13.2%) structural incomplete and 24 (2.3%) indeterminate response one year after initial treatment. Clinical features, management and disease outcome of 91 BIR patients were evaluated. Mean follow-up was 11.8±6.6 years.
Results
All patients underwent total thyroidectomy, 50.5% neck dissection and 97% RAI (122.4±49 mCi). At diagnosis mean age was 48±17 yr, 67% were females and 77% PTC. Mean tumor size was 25±9 mm, with multifocality in 59.3%, ETE 8th in 24.4%, N1 in 43%, stage 8th in I-II 96.6%, and ATA low-risk 69.7%.No patient had distant metastases. Further treatment included: reoperation 20%, additional I^{131} 52% (cumulative 278±135 mCi). During follow-up 53.8% revert to no evidence of disease, 23.1% remained BIR and 23.1% progressed to structural disease. The switch to structural disease could be predicted by older age, ETE, higher ATA risk and advanced TNM 8th stage. PostOp stTg was not a predictor in BIR patients. At the study-end there were 8 deaths (3 disease-related).
Conclusions
Our data suggest that BIR patients have a generally favorable outcome, however up to 23% may progress to structural disease. In this preliminary study we found some variables to be considered as possible predictor factors

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AEP947

The outcomes of thyroglobulin monitoring by high-sensitivity tests after treatment of differentiated thyroid cancer

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The goal was todetermine the optimal methods of postoperative monitoring of serum thyroglobulin (Tg) in differentiated thyroid cancer (DTC). This research intended to compare the prognostic value of immunometric methods with different functional sensitivity (FS) for Tg measurement for detecting recurrent disease.
Design
During 2010–2012 years, 76 patients with treated DTC (a total thyroidectomy and adjuvant radioiodine therapy) were included. All patients were at low-to-intermediate risk group(disease advanced was $T_{1-3}N_{0-1}M_0$), the prevalence of TgAb was 36% ($n=27$).
The study protocol contained the obtaining of samples biochemical markers twice in year: basal Tg on levothyroxine (L-T4) treatment (bTg), Tg after TSH stimulation test (stTg), TSH, TgAb.
In all cases bTg samplings were investigated with immunometric method with functional sensitivity (FS) –0.9 ng/ml and by high-sensitive assays (hs-bTg) with FS ≤ 0.2 ng/ml.
In 80% of patients, TSH stimulation tests were performed by withdrawal of LT4, in other cases through injection of rhTSH.
The observation period is not less than 6 years.
Results
During first 18 months of follow-up, 9 (12%) patients completed the study suffered from treatment failure (it was confirmed by TSH stimulation test – stTg in the range of 4.5–9.7 ng/ml). In these 9 patients the values of hs-bTg were between 0.54–0.89 ng/ml. The observation continued on 67 patients.
The high sensitivity assays confidently predict increases in stTg after withdrawal LT4 in the absence of TgAb. It appears that in TgAb-negative patients with undetectable bTg a negative TSH stimulation test (stTg ≤ 2.0 ng/ml) can be predicted if their hs-bTg ≤ 0.4 ng/ml. TSH stimulation test detected disease recurrence in two TgAb-positive patients with undetectable bTg and hs-bTg was 0.54 and 0.71 ng/ml resp. High-sensitivity Tg tests demonstrated low reproducibility for all TgAb-positive patients, while in TgAb-negative patients all results were reliable. There was no correlation between the level of TgAb and level of basal Tg and treatment failure.
Conclusions
The Tg obtained after TSH-stimulation is still excellent tumor marker.
When TgAb is absent, bTg measurement by high-sensitivity test and neck US are sufficient tools for routine follow-up of patients with DTC – to monitor the bTg trend without performing any TSH stimulation in patients with initial confirmed low-to-intermediate recurrence risk The influence of TgAb significantly reduces the diagnostic value of Tg assessment. When TgAb is present, the monitoring of bTg by high-sensitivity test can't replace completely TSH stimulating test.
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AEP948

Next generation sequencing of 12-gene panel Molecular profiling of Thyroid cancer: An indian study

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Introduction
Next-generation sequencing (NGS) in thyroid cancer allows for high-throughput sequencing analysis of various genetic alterations and provides a useful information of tumor biology. NGS Studies on follicular differentiated thyroid cancer have been scantyfrom Indian subcontinent. In this context, we set out study the prevalence of a genetic panel wide somatic mutations in thyroid cancer.
Material and methods
This prospective study was conducted on 40 paraffin embedded thyroidectomy surgical tissue samples. Institutional ethical committee approval was obtained. Followup details are documented and analysed. Mutation analysis with a 12-gene mutation panel using real-time PCR and ThyroSeq v2 on the Ion Torrent PGM sequencer was employed.
Results
Common single nucleotide polymorphisms (SNPs) with a minor allele frequency of >0.05, asdocumented in dbSNP; noncoding region variants; and variants in repetitive regions were excluded. Mutations were also manually checked using the Integrated Genomics Viewer v2.4.10 to filter out false positives. The analysis found mutations commonly in BRAF (30)), CDKN2A (19), NRAS (12), PI3KCA (17), RET (8), RAS (24) and TP53 (5) genes. The common mutations found in the samples was RET (M918T), NRAS (Q61R), BRAF (V600E) and missense mutation in TP53(c.217–c.1178). A mutation has also been identified in KMT2D gene in two of the patient samples. BRAF, CDKN2A, PI3KCA were more common in papillary cancer; RAS, NRAS, RET mutations were common in follicular cancer; TP53 and KMT2D were seen only in poorly differentiated cancer.

Conclusions
NGS helps in patient management, providing risk stratification and subtyping of malignancy. It can be used in molecular tumor classification, and molecular prediction of recurrence and metastasis in thyroid carcinoma. To the best of our knowledge, this is one of its kind study from Indian subcontinent
Keywords: Thyroid cancer, BRAF gene, RAS gene, genomics, mutation.
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AEP949

Medullary thyroid cancer follow-up in a tertiary center
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Introduction
Although medullary thyroid cancer (MTC) constitutes 2–4% of all thyroid cancers, it is associated with higher mortality compared to differentiated thyroid carcinomas. Here we present long term clinical results of medullary carcinoma patients' follow-up in our center.
Methods and results
MTC was detected in 27 (3.73%) patients of 850 thyroid cancer cases who were followed-up between 2004 and 2020 at the Marmara University School of Medicine, Endocrinology and Metabolic Diseases Department. The mean age at diagnosis was 47.7±14. The female/male (20/7) ratio was 2.8. The mean follow-up was 7.29±4.9 years. In 16 (59.2%) patients, the diagnosis was compatible with medullary thyroid carcinoma in fine-needle aspiration biopsy, the remaining patients were diagnosed after thyroidectomy. The diagnosis was made by biopsy from the supraclavicular lymph node in 2 patients (7.4%), one had no nodule on the thyroid. None of the patients had distant metastases at the time of diagnosis. Neck lymph node metastasis was detected in 8 patients (29.6%) at the time of diagnosis. Relapse occurred in a median of 2 years (min-max: 1–14) after the first surgery in 3 patients (11.1%).
MTC was detected on the right lobe in 12 patients (44.4%), on the left lobe in 13 patients (48.1%), and bilaterally in 2 patients (7.4%). The meantumor diameter was 1.9±1.3 cm. Papillary thyroid microcarcinoma was detected in the contralateral thyroid lobe in 3 patients. The preoperative median calcitonin level was 363.5 ng/l (min-max:5–5655). Median postoperative calcitonin level was 3.3 ng/l (min-max:0.5–871), CEA level was 4.49 ng/ml (min-max: 0.45–14.6).RET mutation was heterozygous positive in 2 patients (7.4%).
Preoperative calcitonin level ($P=0.206$), presence of invasion ($P=0.516$) and tumor diameter ($P=0.581$)was not associated with response rate;on the other hand postoperative calcitonin level ($P=0.0045$) was the only effective factor on remission rate.
In the last visit, 7 (25.9%) patients had a structural incomplete response, and 3 patients (11.1%) had a biochemical incomplete response. 17 (59.3%) patients were in remission, none of the patients died of MTC or another cause.
Conclusion
We observed a higher recurrence rate compared to the literature. In previous studies, 10-year survival was associated with age, disease stage, and postoperative calcitonin levels. Postoperative calcitonin level was the only factor associated with survival in our patients.
Keywords: medullary thyroid carcinoma, calcitonin, life expectancy.
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AEP950

Is Poorly diffentiated thyroid cancer a bridge between well differentiated and anaplastic cancer – Genomic perspective
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Introduction
Poorly differentiated thyroid cancer (PDC) is a relatively rare form of differentiated thyroid caner with intermediate prognosis between well differentiated (WDTC) and anaplastic cancers (ATC). But, this finding is debatable in literature. Genomics is the one of definitive modalities to resolve this conundrum. ATC tends to express P53 and KMT2D mutations frequently, while WDTC have no such mutations. Similar studies are scanty in PDC. In this context, we set out study the prevalence of these somatic mutations in surgical tissue samples of PDC.
Material and methods
This prospective study was conducted on surgically managed thyroid cancerpatients. Institutional ethical committee approval was obtained. Diagnosis was based on biochemical confirmation, imaging, fine needle aspiration cytology and later confirmed by histopathology. We selected 10 PDC, 3 ATC and 25 WDTC cases. Tumour tissue samples were taken from ex-vivo thyroidectomy specimen within operation theatre. After appropriate processing of samples, DNA extraction, cDNA preparation, PCR amplification, application of 2 sets of Primers were performed as part of mutational analysis of P53 and KMT2D genes.
Results
Heterozygous mutations in KMT2D gene and missense mutation in P53 genewere found in 3/10 (30%) and 5/10 (50%) of PDC cases respectively. In ATC, KMT2D mutations were seen in 2/3 (67%) and 3/3 (100%) cases. In WDTC, mutations were not seen in either of these two genes.
Conclusions
Our study shows a distinct chronological pattern of mutations in KMT2D and P53 genes suggesting correlation between the gene function and cancer cell differentiation. Further, PDC appears to be intermediate in mutation frequency, with WDTC on lower side and ATC on higher side of scale. Though our results are not robust, it sets precedent for larger multi-institutional studies to justify this observation in future.
Keywords: thyroid cancer, poorly differentiated cancer, anaplasia, follicular cell.
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AEP951

The importance of molecular-genetic examination in a patient with sonographically suspected but cytologically benign thyroid nodule
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Introduction
Differential diagnosis of thyroid nodules is one of the most frequently solved problems in the endocrinological practice. It is always necessary to determine their biological nature, which will decide about further therapeutic procedure, especially about early surgery in case of proven malignancy. In addition to sonographic examination and fine needle aspiration biopsy (FNAB), now we can also use the possibilities of molecular-genetic examination.
Case report
We present a case report of a 55-year-old woman sent to our institute to examine the sonographically suspected nodule in the right thyroid lobe. In accordance with conventional procedures, fine needle aspiration biopsy of the nodule was performed. The cytological examination determined the sample as benign (Bethesda Category II). Due to sonographically very suspicious features (microcalcification, TI-RADS category 5), we performed molecular-geneticanalysis for the presence of genetic mutations associated with thyroid oncology. The somatic mutation of V600E in the 15th exon of the *BRAF* gene was proven. This mutation is associated with papillary thyroid carcinoma (PTC) and with a worse prognosis of the disease. Based on these findings, we indicated the patient to undergo total thyroidectomy. Histological examination confirmed PTC and also the mutation in the *BRAF* gene was identified in surgical tissue. The patient continues to be observed at our institute and simultaneously at the Department of Nuclear Medicine and Endocrinology in Motol University Hospital, where the first dose of radioiodine has already been given.
Conclusion
The benefit of our workplace lies in a complex diagnostic approach. Although according to the ETA guidelines molecular-genetic testing of FNAB-derived material is recommended only in Bethesda III and above,

our case report shows that a well-performed thyroid sonography leading to suspected malignancy should be complemented by a molecular-genetic examination of the nodule despite benign cytological analysis. The *BRAF* V600E mutation is specific for PTC, therefore its finding in the presented patient led directly to the diagnosis of PTC.

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AEP952

Intraoperative navigation of the parathyroid glands in the surgical treatment of highly differentiated thyroid cancer

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Topicality

The most common cancer of the endocrine system is thyroid cancer. The main method of treatment for highly differentiated thyroid cancer is surgical. A special place among the complications of surgical treatment of thyroid cancer according to the severity of manifestation and the complexity of prevention is occupied by postoperative hypoparathyroidism.

The purpose of the study.

Minimize the risk of damage to the parathyroid glands during thyroid surgery.

Inclusion criteria – patients with highly differentiated thyroid cancer T1-4aN1a-1bM0-1.

Exclusion criteria – highly differentiated thyroid cancer T1-2N0M0patients.

Materials and methods

The object of the study was 163 patients with highly differentiated thyroid cancer treated in the Samara Regional Clinical Oncology Center from July 2017 to September 2019. The average age of patients in the main group (thyroidectomy + selective cervical dissection using the pharmaceutical preparation 5-aminolevulinic acid hydrochloride) was 68.5 ± 25.6 years (18–82), 84 patients in total, in the control group (thyroidectomy + selective cervical dissection)) – 64.9 ± 24.5 years (21–78) of a total of 79 patients. In order to evaluate the effectiveness of parathyroid gland preservation, the level of parathyroid hormone was monitored on days 7, 25–30 and 55–60 after surgery and calcium, ionized calcium, phosphorus on 1, 7, 25–30, 55–60 days after surgery. Patients of the main group in the preoperative period were orally prescribed to take the 5-aminolevulinic acid hydrochloride drug twice – 3 hours before the start of surgery at a dose of 20 mg/kg (180 ± 15 min), then – 1 hour before surgery at a dose of 10 mg/kg (60 ± 10 min). Intraoperatively, to detect the parathyroid glands, an optical radiation source with a wavelength in the range from 385 to 460 nm and polarizing glasses were used, when fluorescent sites were detected, an urgent cytological study was performed to confirm parathyroid gland visualization.

Results

In the main group, transient hyperparathyroidism was observed in 2 patients (2.3%), stopped in 7 days. Persistent hypoparathyroidism was absent in patients of the main group. In the control group, transient hypoparathyroidism wasobserved in 12 patients (15.1%). Persistent hypoparathyroidism was observed in 2 patients (2.5%) in the control group.

Conclusions

Intraoperative navigation of the parathyroid glands using the pharmaceutical preparation 5-aminolevulinic acid hydrochloride can significantly reduce the number of postoperative complications associated with the removal/damage of the parathyroid glands.

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AEP953

Diagnostic patterns of relapsed differentiated thyroid cancer (DTC) and the efficacy of rescue therapies (ERUDIT Study)

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Introduction

Advanced differentiated thyroid carcinoma (aDTC) – herein defined as locally unresectable or metastatic disease – is one of the most common late-stage endocrine neoplasias. However, available data about its natural history is limited. ERUDIT is a multicenter, observational, retrospective study of patients diagnosed with aDTC in Spain and Portugal. The study describes its natural history from the initial diagnosis until the advanced stages of disease, focusing on specific characteristics of this subpopulation of DTC, as well as its treatment, response patterns and medical specialties involved in its management.

Objectives

To describe diagnostic demographics of DTC patients whose disease have relapsed after initial treatment, the usage patterns and efficacy of rescue therapies, and the medical services involved in patient care.

Materials and methods

Clinical records from patients ≥ 18 y-o diagnosed with aDTC (including poorly differentiated DTC) with first evidence of advanced disease documented between January 2007 and August 2017 were retrospectively reviewed until death or lost to follow-up.

Results

213 patients were identified in 23 centres. Median age at initial diagnosis was 63 y-o, 59% were females. During the follow-up 46% progressed to advanced disease through previous relapse episodes after first treatment (surgery ± 131radioiodine [RAI]). Median (95% CI) relapse-free survival (RFS) from the initial treatment was 2.3 (1.7–2.9) years. Computed tomography (CT) and whole-body scan (WBS) were the most commonly used methods for relapse diagnosis (59% and 29%, respectively), being metastatic in 90% of the cases. Most frequent localization was lung (41%), and the rescue therapies, when indicated, were mainly RAI (62%) and surgery (14%). Specifically, 20% of the patients treated with RAI received up to 3 courses with median dose of 138 mCi each and cumulative dose of 518 mCi. Persistent structural disease was frequently reported after RAI (average 15% after three doses). Use of ablative interventions and radiotherapy was anecdotal (5%). Post relapse radiological follow-up mostly relied on CT (38%), positron-emission CT (18%), and WBS (16%). Endocrinology was the leading medical specialty responsible for patient monitoring (61%), while two thirds of the patients were evaluated by multidisciplinary committees.

Conclusions

Almost half of this cohort of aDTC tumours progressed onto advanced stage through previous relapses, with median RFS of 2.3 years and 62% being RAI-treatable. From this group, still 15% shows persistent disease after three RAI treatments. This suggests an unfavorable atypical evolution of some aDTC already since their initial treatment stages.

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AEP954

TNM 8th edition in thyroid cancer staging: Is there an improvement in predicting recurrence?

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TNM 8th edition introduces changes in the staging of patients with differentiated thyroid carcinoma (DTC). This study aims at assessing the ability of TNM 8th edition in predicting structural recurrence of DTC.480 DTC patients were retrospectively evaluated by 7th and 8th editions of TNM staging systems in relationship with risk stratification, response to therapy and recurrence of disease as defined by 2015 American Thyroid Association (ATA) guidelines. As compared to the 7th edition, TNM 8 led to downstage 136 patients (28.3%), with 97.5% of patients falling into lower stages (I-II) and only 2.5% remaining in higher stages (III-IV) ($P<0.001$). Patients who were downstaged in stages I-II by TNM 8 were classified more frequently at intermediate-high risk ($P<0.001$), had more frequently structural incomplete response to therapy ($P=0.009$) and had higher risk of structural recurrence ($P=0.002$) as compared to patients who were in the same TNM stages but were not downstaged. Specifically, the risk of structural recurrence was significantly high in patients in whom the downstaging was induced by changes in tumour classification [Hazard ration (HR) 6.18, C.I. 95% 2.20–17.40; $P=0.001$] but not in those who were downstaged for the increase in age cut-off (HR 2.80, C.I. 95% 0.86–9.19; $P=0.09$). In conclusion, TNM 8th edition did not show reliability in predicting aggressiveness of DTC. In fact, the downstaging of DTC patients especially when performed due to changes in tumour classification may overlook patients predisposed to structural recurrences, potentially causing uncertainty in the therapeutic decision-making at the time of disease's diagnosis.

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AEP955

A study of the relationship between RET/PTC and Cyclin D1 expression of the thyroid under autoimmune thyroiditis and Papillary thyroid carcinoma (PTC): Clinical-pathological correlation

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Our research subject is to study the importance of some favorable molecular biological markers for prognosis of premalignant characteristics of Hashimoto's thyroiditis (HT) parenchyma. To clarify the pathogenetic link between these two pathologies (HT, PTC), we choose markers, indicating, at the one hand, on the tumor cell cycle, such Cyclin D1, at the second hand, RET/PTC rearrangement in HT, in order to determine molecular changes, connecting Hashimoto's thyroiditis with Papillary thyroid carcinoma (PTC). Basic of these concepts are follows: 1. We hypothesized, that Cyclin D1 diffuse immunoreactivites should play a role of PTC malignancies due to the mechanism of gene amplification in HT at first, while the chromosome 6p21 triggered activation of chromosome 11q23 (Cyclin D1 gene location); normal thyroid follicular cells do not show immunoreactivity for Cyclin D1 on immunohistochemistry, but Cyclin D1 is over expressed in up to 60% of PTC. 2. RET/PTC proto-oncogene is located on the long arm of chromosome 10. In the PTC pathogenesis activation of RET includes rearrangement or gene redistribution and should be typically more sensitive method of PTC detection in setting of HT. The research database includes postoperative surgical pathology material obtained 150 cases from 1065 patients, who had undergone total thyroidectomy, lobectomy, and partial resection of the thyroid gland. We reviewed all continuous thyroid histopathological reports from 2016 to 2019 years. The mean age was of 49.5 years (range 23–76). This study was reviewed and deemed exempt from written informed consent by the Ethics committee and Board of medical sciences at Tbilisi State University based on Helsinki-ethical principles declaration for medical research (2013). Immunohistochemical (IHC) studyincludes following markers: 1. Cyclin D1 (clone D-6, 1:50, Dako), 2. Ret Antibody (6E4C4, Santa Cruz Biotechnology, U.S.A.). Results were shown statistically significant correlation between RET/PTC proto-oncogene expressionin HT follicular cells nuclei and frequency of follicular epithelial dysplasia areas (χ^2-test: $P=0.091$; Fisher exact test: $P=0.119$). In terms of Cyclin D1 activity, according data, this cells cycle marker is not crucial for the detection of malignant transformation into thyroid Hashimoto parenchyma (χ^2-test: $P=0.012$; Fisher exact test: $P=0.017$). These results confirmed the importance of Cyclin D1 and RET/PTCproto-oncogene expression, suggesting their malignant transformation in the evaluation of HT behavior.

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AEP956

Medullary Thyroid Carcinoma (MTC); unusual metastatic sites. Two case reports

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Background
MTC tends to metastasize early in the course of the disease affecting usually regional lymph nodes; in 7–23% of patients distant metastases may be present at diagnosis (common metastatic sites:liver, lungs, bone). We present two MTC cases with unusual metastases to the breast, pancreas and mandible.
Case presentation
Patient No 1
A 48-year-old female was diagnosed with MTC in 1990. Total thyroidectomy was performed followed by neck dissection. Ten years later, cervical and mediastinum lymph node dissection took place. In 2009, disease progression was confirmed by elevated Calcitonin and CEA levels along with a positive uptake (Octreoscan) in mediastinum and liver. A bone scan revealed additional metastases in the thoracic spine and external bone radiotherapy and liver chemoembolisation were performed. In 2013, mediastinum MRI revealed a lesion in the right breast confirmed by mammography. Histology of breast tumorectomy confirmed MTC metastasis and treatment with vandetanib was initiated.
Patient No 2
A 55-year-old female was diagnosed with MTC in 2003. Total thyroidectomy with neck dissection was performed. Due to cervical nodal metastases, she underwent modified radical neck dissections. In 2014, recurrent metastatic disease in the right shoulder was confirmed by MRI and external radiotherapy was performed. Furthermore, an abdominal MRI revealed a head pancreatic tumor. MTC metastasis was confirmed by biopsy and treatment with vandetanib was initiated. Additionally, the histology of a resected painful mass in the right mandible revealed a well differentiated MTC.
Conclusions
These two MTC cases, although apparently rare, highlight the need for watchful care and prompt recognition of unexpected metastases in MTC patients.

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AEP957

A novel method for detecting autoantibody to wd repeat domain 1: Clinical application for differentiating papillary thyroid carcinoma with poor clinical outcome

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Background
Papillary thyroid carcinoma (PTC) is known as the most common histological subtype of thyroid carcinoma. The prognosis of PTC is generally favorable. However, small number of patients with PTC progressed with distant metastasis and invasion to adjacent organs. New diagnostic tool for early detection of PTC with poor outcome is desired. We previously reported that autoantibody to WD repeat domain 1 (AWA) in the serum was associated with the existence of undifferentiated thyroid carcinoma (UTC) and PTC (Izawa S *et al.*, Clin Endocrinol 2013). The objective of our study is todevelop this assay to be sensitive and specific for differentiating PTC with poor prognosis.
Materials and methods
A peptide library (peptide length = 12 aa, off-set = 6 aa) originated from human WDR1 isoform 1 were firstly screened (1st screening) by the serum of 3 patients with UTC and 3 normal healthy controls (N). Furthermore, 2nd screening was performed for selecting candidate peptides by using another peptide library (peptide length = 12 aa, off-set = 2 aa) designed by the result of 1st screening. Finally, candidate peptides were evaluated to be hydrophilic by bioinformatics. Sera from 16 patients with advanced thyroid carcinoma (UTC and PTC with metastasis and/or invasion to adjacent organs), 8 with not advanced PTC (without metastasis and invasions to adjacent organs), 14 with benign thyroid nodules (B), 15 with autoimmune thyroid disease (A), and 7 N were evaluated by ELISA using 12 candidate peptides.
Results
A total number of 42 peptides for detecting high titer of AWA were selected by the 1st screening. Most of these peptides were located in the C terminal of WDR1 isoform 1. After finishing 2nd screening, 12 candidate peptides with hydrophilic sequences were selected for ELISA. A peptide originating from human WDR1 isoform 1 (WDR1 2–33) presented significantly higher ($P < 0.05$) titer of AWA in advanced thyroid carcinoma (0.621 ± 0.289) than not advanced PTC (0.326 ± 0.114), B (0.255 ± 0.142), A (0.318 ± 0.164), and N (0.303 ± 0.161). The diagnostic performance of WDR1 2–33 was superior to other 11 peptides by ROC analysis.
Conclusion
We demonstrated that WDR1 2–33 could be a peptide containing the epitope of AWA. Our data suggested that evaluating AWA by WDR1 2–33 might be a new diagnostic method for early diagnosis of PTC with poor prognosis (patent pending JP2018–045806).

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AEP958

The profile of patients with hyperthyroidism at a tertiary health care center in the oriental region of northeastern Morrocco: – A study of 186 cases -

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Introduction
Hyperthyroidism is characterised by an increased hormone synthesis, with non-specific and pleomorphic clinical features. Management strategy, depends entirely on the etiological status ; as part of an holistic vision. The purpose of this study is to shed light on epidemiological, clinical, etiological and therapeutic aspects of hyperthyroidism in Endocrinology & Diabetology department of Oujda's Mohammed VI university hospital.
Material and methods
Prospective data analysis of patients with hyperthyroidism followed up in Endocrinology & Diabetology department of Oujda's Mohammed VI university hospital.
Résults
186 patients were enrolled in the study. The overall mean age was 43.9 years old with a female predominance (83.9%). 18.7% of the patients had a family history of dysthyroidism. Clinicalhyperthyroidism features have been considered as the presenting complaint in 67% of all the cases, and thyroid orbitopathy have been noticed in 15.6% of patients. The mean serum concentrations of Ultrasensitive TSH and free T4 were around 0.09 mUI/l and 50.4 pmol/l respectively. Clearly elevated Thyrotropin Receptor antibodies (TRAb) and Anti-Thyroid Peroxydase antibodies (anti-TPO) were noticed in 52.4% and 45.1% of cases respectively. Grave's disease and toxic nodular goiter were identified in 61.4% of the patients, as the 2 major etiologies of thyrotoxicosis in our study. 97.8% of the patients underwent antithyroid drug therapy, and b-adrenergic blocker was added basically in 42.5% of the cases. Neutropenia was observed only in 3.9% of the patients. A total thyroidectomy was proceeded in 36.4% of cases and 31.1% preferred Radio Iodine (I-131) therapy.
Conclusion
Hyperthyroidism is considered as a frequent endocrinopathy which can be easily diagnosed. However,chosing an eminent therapeutic pathway remains a matter of debate and a challenge for every clinician.

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AEP959

Features of large intestinal microbiota of patients with hypothyroidism

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Introduction
The prevalence of manifest hypothyroidism by various data is 0.2–2%, sub-clinical – up to 3% in men and up to 10% in women, and in people over 70 years old – 13–14%. The presence of concomitant gastrointestinal diseases significantly limits the possibility of hypothyroidism compensation; these patients need higher doses of levothyroxine. According to a number of researchers, hypothyroidism is often accompanied by small intestinal bacterial overgrowth (SIBO). The purpose of the work was to study the species composition and population level of microflora of the intestinal cavity in patients with primary hypothyroidism depending on disease compensation, as well as study of the content of the main filotypes of intestinal microbiota in these patients.
Material and methods
44 patients with hypothyroidism (19 men and 25 women) aged 30–72 years (the average age 47.3 + 8.9 years) were examined at the stageof compensation and decompensation of the disease and 51 practically healthy people who formed the control group. Due to the disease compensation, 2 groups of patients were created. The first group (20 patients) consisted of patients in the state of compensation, the second group (24 patients) – in the state of decompensation of the disease. Identification of selected cultures was carried out according to morphological, tinctoral, cultural and biochemical properties.
Results and discussion
The dysbiosis of the IV degree was established in 34 (77%) patients, the third degree — at 8 (18%) patients, II degree — in 1 patient, I degree — in 1 patient. Imbalance developed due to eliminations and deficiency of autochthonous anaerobic, obligatory bacteria (*Bifidobacteria, Lactobacteria*), contaminations of the large intestine by enterotoxigenic, enteropathogenic and hemolytic *Escherichia*, opportunistic enterobacteria and an increase of the number of the bacteriodes, peptococci, peptostreptococci, clostridia, staphylococci and yeast-like fungi of the *Candida* type.
Conclusion
It is found out that the relative content of the main microbial filotypes differed from healthy subjects compared with patients with hypothyroidism. Thus, *Firmicutes* content in patients with hypothyroidism was significantly higher and bacteroides content – significantly lower in relation to healthy individuals ($P < 0.05$). Analyzing the content of the main microbial filotypes depending on the state of hypothyroidism compensation, it was found that in patients in the state of compensation and decompensation of hypothyroidis, *Firmicutes* content was significantly higher ($P < 0.05$), and the content of *Bacteroides* – relatively lower in patients in the compensation state comparing to the group of healthy people ($P < 0.05$).

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AEP960

Comparative characteristics of NAD(P) – dependent dehydrogenases in blood lymphocytes and neutrophils in patients with Graves' disease

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Background
Thyroid hormones participate in maturation, differentiation and triggering of immunity, but little is known about the modulating role of thyroid hormones on intracellular enzymatic reactions of immune cells and their role in immunopathogenesis of Graves' disease (GD).
Methods
The activity of NAD(P)-dependent dehydrogenases in lymphocytes and neutrophils ofperipheral blood was studied in a group of 145 women with GD, 53 (36.5%) patients with a first episode and 92 (63.4%) with relapse of hyperthyroidism, mean age 43.14±13.81 years, and, also, 73 age- and gender matched healthy controls were determined. The diagnosis of GD had to be established by a low TSH, a high fT4 or fT3 and positive TRAb. The activity of glycerol-3-phosphate dehydrogenase (Gly3PhD), glucose-6-phosphate dehydrogenase, NAD-lactate dehydrogenase (LDH), NADH-lactate dehydrogenase (NADH-LDH), NAD–malate dehydrogenase (MDH), NADH–malate dehydrogenase, NAD-glutamate dehydrogenase (GDH), NADH-glutamate dehydrogenase (NADH-GDH), NAD(P)-isocitrate dehydrogenases (ICDH and NADP-ICDHrespectively), NADP(H)-glutamate dehydrogenases (NADP-GDH and NADPH-GDH respectively), NADP-malate dehydrogenase and glutathione reductase were measured usingbiochemiluminescence method.
Results
Studying the activity ofNAD(P)-dependent dehydrogenases in lymphocytes we found the reduction of MDH and NADPH–GDH ($P<0.001$). In neutrophils ofperipheral blood in patients with manifestation of GD increased the activity of ICDH ($P<0.01$) and reverse reaction of LDH ($P<0.05$). In patients with GD relapsing in peripheral blood lymphocytes we observed low activity of LDH ($P<0.05$), MDH ($P<0.01$), ICDH and NADPH–GDH ($P<0.01$). Studying intracellular metabolism of blood neutrophils patients with recurrence of the disease showed significantly high activity of NADP-MDH, NADP-GDH, NADP-ICDH, GDH, NADH-GDH, but inhibiting reverse reactions of LDH and MDH ($P<0.05$). The comparative analysis of the studied NAD(P)-dependent dehydrogenases demonstrate, that in group with newly diagnosed GD compared to patients with recurrent disease in lymphocytes of peripheral blood increase the level of Gly3PhD, NADH-GDH ($P<0.05$). Intracellular metabolism of blood neutrophils in patients with manifestation of GD compare to GD relapse group vary by decreasing activity of Gly3PhD,GDH and NADP-MDH ($P<0.05$).
Conclusion
The main features oflymphocyte metabolism in GD relapse patients were the reduction of intermediates formation for macromolecular synthesis reactions and aerobic processes, the low intensity of glycolysis, nitrogen metabolism,and in neutrophils – activation in the system of malate-aspartate hydrogen shunt. Further exploration of immunological mechanisms has the potential to improve treatment of GD, with more targeted treatment strategies based on the different physiopathological concepts of this heterogeneous disease.

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AEP961

Chronic autoimmune thyroiditis and hypovitaminosis D – mammary eco-structural implications

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Introduction
Benign breast disease is the most common reason for senology consultation.
Objectives
To investigate the possible involvement of thyroid autoimmunity and hypovitaminosis D in the development of mammary echo-structural lesions.
Method
The BI-RADS score was assigned to categories 1–4 characteristic of benign mastopathy, in three groups of patients: Group 1 (n=167) – with chronic autoimmune thyroiditis and normal vitamin D values; Group 2 (n=172) – patients without thyroid pathology with moderate and severe vitamin D deficiency; Group 3 (n= 181) – patients with chronic autoimmune thyroiditis and moderate and severe vitamin D deficiency respectively.
Results
In the study group 1–90% of patients had both types of antithyroid antibodies (ATPO/ATG) and 6.5% only positive ATPO, and 3.5% only positive ATG; for the patient group with both types of antibody there were significant differences ($P<0.001$) between the BIRADS score 4 and previous scores 1–2–3; statistical significance was remarkable in the ATG group ($P<0.001$) and not significant for the ATPO group. In group 2 of study – a statistical significance ($P<0.001$) was found in both groups of women investigated in terms of serum deficiency of vitamin D, for stage 4 BIRADS score, the statistical significance ($P<0.001$) also being in favor of those with very low levels of vitamin D. For study group 3 – the maximally breast density assessed in the study (BIRADS-4) was significantly increased ($P<0.001$) for patients from the group with moderately low vitamin D level with both types of antibodies and with positive ATPO only, being insignificant in the group with positive ATG – only. For the severely deficient group the statistical significance was recorded only in the group with both types of thyroid autoantibodies. Within each study group, significant percentages ($P<0.001$) for the 4-BIRADS score in the group with both antibody types present – group 1 and group 3 moderate and severe vitamin D group were observed.
Conclusions
The presence of thyroid autoimmunity and vitamin D deficiency are factors involved in the development of benign mastopathy. Additional studies may be required to fully characterize the mechanism of action. Theexpression specificities of autoimmunity and functionality of vitamin D receptor, their quantitative fluctuations in breast tissue and the specificity of bioavailability of mammary tissue components offer lesion variability with multiple individualities.

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AEP962

Renal malfunction in patients with primary hypothyroidism

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Aim
Study the correlation between leptin and renal malfunction in patients with primary hypothyroidism (PH).
Methods
161 patients suffering from PH took part in the investigation. Criteria of choice were as follows: patients' age from 36 to 60 and presence of PH. Presence of any acute or chronic renal disease or ischemic heart disease was the criteria of exclusion. The diagnosis was made on the basis of complaints, family history, typical clinical sign of manifested hypothyroidism and was confirmed by the results of hormonal analyses.
Results
Among 152 examined patients, barrier malfunction was found in 52.6% of patients, out of which 46.6% had albuminuria, and 6% had proteinuria. Early stage of nephropathy was found in 24% of patients. Patients diagnosed with abnormal renal function were divided into four groups taking into account their body weight index (BWI), since this factor has a significant effect on changes in mentioned above parameters. Patients with PH on the basis of Hashimoto thyroiditis with BWI<24.9 kg/m^2 and BWI>25 kg/m^2 were included to IA and IB groups correspondingly. Group II A and II B encompassed patients with postoperative hypothyroidism (PH) with BWI<24.9 kg/m² and BWI>25 kg/m^2 correspondingly. At the same time, calculating RGF by MDRD formula considering sex and age, its value was found to be quite low (77.99±2.18) and essentially differed from the data received in the control group. Patients with PH and excessive body weight showed much lower RGF in comparison to control group ($P<0.001$). Evaluating the leptin level it was noted that the bigger body weight patients with PH had the higher concentration of leptin in blood serum was revealed. Thus, patients with hypothyroidism and Hashimoto thyroiditis had leptin level two times higher in the group with BWI>24.9 kg/m^2 than in the group with BWI<24.9 kg/m^2, and in the group of patients with PH this level is three times higher. Hyperleptinemia is closely related to anthropometric indices and functional parameters of kidneys. The most distinct reverse contact was traced between leptin and RGF and direct contact–among waist circumference, BWI and albumin secretion.
Conclusion
Patients with manifested hypothyroidism have revealed renal malfunction, predisposed by such risk factor as hyperleptinemia, overweight and abdominal obesity.

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AEP963

The possibilities of sonography in the diagnosis of thyroid nodules

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Purpose
To study the possibilities of sonoelastography (SEG) in the diagnosis of thyroid tumors. Materials and methods: in 123 patients (27 with papillary thyroid cancer, 45 with thyroid adenomas, and 51 with colloid goiter), different versions of SEG were used at the preoperative stage: compression sonoelastography (CEG) and point shear wave elastography (ARFI). Together with the staining assessment, quantitative parameters were determined: the speed of the transverse wave (M), and the Young's modulus (E). When using point elastography of the shear wave, the velocity of the transverse wave in m/s was measured.
Results
Normal thyroid tissue with CEG had slightly inhomogeneous, uneven fine-grained symmetrical staining with red-yellow tones. With nodular goiter, the staining zones of different colors and intensities were determined, depending on the' stiffness ' of the tissue in the node. Two-color (51.3%) and three-color (33.3%) staining prevailed in the CEG of colloid nodules. The ARFI in thyroid nodules was 3.11 ± 0.75 m/s, and the Young's modulus was 19.37 8.4 kPa.
The thyroid adenomas had different color characteristics and greater variety. Two-color staining occurred in 26.3% of observations, and four-color staining occurred in 47.2%. It was mostly green (58.2%). For ARFI in these tumors presented the cross-wave velocity was 3.96 ± 0.75 m/s, and the Young's modulus was 35.3 ± 7.4 kp. In most cases, purple-blue-blue staining (76.4%) was detected in the verified RSC. Four-color (26.3%) and five-color (35.2%) coloring prevailed, with a predominance of cold-tone patterns. The ARFI for thyroid cancer was 4.77 ± 0.84 m/s, and the Young's modulus was 61.22 11.3 kPa. The predictive ability of SEG in the differential diagnosis of thyroid tumors was evaluated using ROC analysis. The model took into account qualitative variables that affect the result. The index AUC = 0.811 (95% CI = 0.765–0.833), indicates that the compression sonoelastography is a test with good quality, but has limits on specificity, which is important in the diagnosis of thyroid cancer. When evaluating ARFI using ROC analysis, it was found that AUC = 0.822 (95% CI = 0.787–0.853). The sensitivity of ARVI was higher than that of KG (87.8%), and the specificity was equal (80.5%). The results obtained were better than the CEG indicators, but the differences were not reliable ($P > 0.05$). It is difficult to assess microcarcinoma and follicular thyroid cancer, in which both ARFI have low sensitivity and specificity. This reduces the diagnostic effectiveness of the test.

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AEP964

Efficacy & safety of total thyroidectomy as preferred primary treatment option for Graves' disease

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Graves' disease is a common autoimmune condition, and the most common cause of hyperthyroidism. A number of definitive treatment options for this disease exist, including radioiodine (RI) and surgery. Surgery is often reserved for patients for whom RI is contraindicated or who have previously failed other treatments, including radioactive iodine ablation (RIA). The aim of this study was to assess the efficacy and safety of total thyroidectomy at our institution as a preferred primary treatment option for patients with Grave's Disease. A total of 98 consecutive cases of total thyroidectomy for the primary treatment of Grave's Disease were analyzed. Patients assessed in our retrospective study had a very low rate of complications and there was no mortality. There were no cases of voice disturbance associated with recurrent laryngeal nerve injury. The rate of hypocalcemia (transient 11.3%; persistent beyond 6 months 1%) was low and there was only one return to the operating room for evacuation of hematoma. The only patient with more persistent hypoparathyroidism recovered her parathyroid hormone levels at 18 months. Patients' symptoms, including symptoms related to hyperthyroidism, pressure related symptoms and ophthalmopathy, significantly improved in the follow up period. 17.2% of patients in this study had papillary cancer incidentally present in the surgical specimen on pathology. This study provides evidence that in selected patients with Graves' disease, surgical management with total thyroidectomy should be considered a safe and effective first line treatment. It provides complete and safe cure of disease and rapid resolution of symptoms. In addition, in our study, the simultaneous excision of incidental papillary cancer was a significant added benefit of total thyroidectomy.

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AEP965

Constitutive activation of Nrf2 antioxidant pathway leads to age-dependent goiter and compensated hypothyroidism in mice

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Background
KEAP1 gene (Kelch-like ECH-associated protein 1) that encodes the main inhibitor of nuclear factor erythroid 2-related transcription factor 2 (Nrf2), a central mediator of antioxidant responses, has been found to be one of the mutated genes that lead to familial multinodular goiter (MNG). The proposed association of *KEAP1* with familial MNG is based on only two loss-of-function mutations in respective Japanese families. To date, there is no experimental evidence from model organisms to support that decreased Keap1 levels can cause goiter.
Hypothesis
We hypothesized that enhanced Nrf2 signaling induced by reduced Keap1 expression in mice can lead to goiter.
Methods
Male Keap1 hypomorphic C57BL/6J male mice that express ~80% less Keap1 in their tissues (Keap1 knockdown mice:'Keap1KD') were studied at 3 and 12 months of age and compared to wild-type mice (WT).Plasma, thyroids and pituitary glands were collected for assessment of thyroid function and for histology as well as gene and protein expression by quantitative PCR and immunoblotting respectively.
Results
Keap1KD showed diffuse goiter that began to develop in early adult life and became highly prominent at the age of 12 months when the thyroids of Keap-1KD were six-fold heavier than WT. Histomorphometry assessment of thyroids showed that Keap1KD had ~three-fold larger follicle area and colloid compartment but no thyroid nodules or hyperplasia was detected. Keap1KD also showed primary hypothyroidism already in early adult life that was eventually well-compensated over time by increased TSH levels (at age of 12 months: WT TSH = 47.7 ± 9.1 mU/l, Keap1KD TSH = 460 ± 74 mU/l). This was also reflected in the pituitary gland of Keap1KD where *Tshb* mRNA was ~three-fold higher than WT. Despite a known stimulatory effect of Nrf2 on Tg gene transcription and Tg protein abundance, these measures were decreased in the thyroid of Keap1KD mice. No clear patterns were observed in the expression profiles of other thyroid hormone synthesis-specific factors, such as *Duox1, Duoxa1, Duox2, Duoxa2, Tpo, Nis, Dio1, Dio2, Dehal1* mRNA levels, with the exception of Tg-processing and Tg-degrading cathepsins, including an increase in mature forms of cathepsins D, L and S.
Conclusions
Keap1KD mice showed age-dependent diffuse goiter and compensated hypothyroidism. The precise mechanism accounting for the thyroidal phenotype remains to be elucidated, but it may involve enhanced Tg solubilization and excessive lysosomal Tg degradation. This study unravels novel roles of the druggable Keap1/Nrf2 pathway in thyroid function and economy.

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AEP966

Low serum IL-17A in pregnancy during second trimester is associated with an increased risk of subclinical hypothyroidism

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Problem
Interleukin-17A (IL-17A) has a role in sustaining normal pregnancy. IL-17A isalso associated with thyroid autoimmunity during pregnancy. This study sought to investigate whether IL-17A is a risk factor for thyroid dysfunction during pregnancy without thyroid autoimmunity.
Methods of study
The study comprised 216 pregnant women with negative thyroid peroxidase antibody (TPOAb) andthyroglobulin antibodies (TGAb) during the second trimesterwho provided samples for serum IL-17A and thyroid function detection. To further evaluate the ratio of CD4+IL-17A+Th17 cells, we collected peripheral blood from 26 participants with thyroid-stimulating hormone (TSH) levels 2.5 mIU/l and 26 pregnant-week matching populations with TSH levels >2.5 mIU/l, along with samples from 20 participants with TSH levels ≤4 mIU/l and 20 pregnant-week matching populations with TSH levels >4 mIU/l.
Results
The serum IL-17A levels and ratios of CD4+IL-17A+cells were significantly lower in women with TSH>2.5 mIU/l than in those with TSH≤2.5 mIU/l (both $P<0.01$). Similar lower differences were noted in women with TSH>4 mIU/l (subclinical hypothyroidism) than in those with TSH≤4 mIU/l (both $P<0.01$). The IL-17A level ($\beta=-0.195$, $P=0.004$) and week of gestation ($\beta=0.284$, $P=0.000$) were significant predictors of regression, with TSH as the dependent variable in all participants during the second trimester. Logistic regression indicated that a lower serum IL-17A level was a risk factor for TSH>2.5 mIU/l [OR=0.453 (0.298–0.689),$P=0.000$] and subclinical hypothyroidism [OR=0.588(0.385–0.899), $P=0.013$].
Conclusion
A low serum IL-17A level during the second trimester is associated with an increased risk of TSH>2.5 mIU/l and subclinical hypothyroidism.

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AEP967

Management and outcomes of graves' disease – a retrospective audit

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Background
Graves' disease is a common cause of thyrotoxicosis,especially amongst females. In the UK,initial treatment is usually with anti-thyroid drugs, using either a 'block and replace' or a titrating regime. A meta-analysis suggests about 50% chance of relapse after the initial course of treatment and may then require definitive cure with radioactive iodine or surgery.
Method
A retrospective audit of patients with Graves' disease attending our endocrine clinics from 2016–2018 was conducted, to study our medical management of this condition and the rate of relapse. The European Thyroid Association Guideline for the management of Graves' Hyperthyroidism was used as the standard.
Results
A random selection of 36 patients with Graves' disease was audited. About 70% were female, and the age ranged 27–73 years. Almost three quarters of the audited patients had completed treatment, while the rest were still on treatment and 1 patient was lost to follow-up. Mean duration of treatment was 17 months. All but one patient had thyroid antibodies checked early during treatment, and these were elevated, however only 13 patients had them rechecked prior to stopping treatment. The titrating regime was used in 64% and the 'block and replace' regime in 36%, however a few patients were switched between the two regimes during treatment. About 38% (n= 10/26) of patients had relapsed and of these, half did not have antibodies retested prior to withdrawal of treatment. Where they were rechecked, the mean TSH receptor antibody was 9.41 IU/l (normal range <1.22 IU/l) prior to stopping treatment. Four of the ten patients that relapsed had been on a 'block-and-replace' regime while six had been on a titrating regime. Definitive treatment (radioactive iodine or surgery) was offered to 16 patients due to relapse or difficulty in stopping treatment.
Conclusions
Our relapse rates appear to be lower than in other studies, possibly because the period of follow-up was limited to the audit period. The titrating regime appears more popular amongst the six Consultants but there was no convincing evidence of superiority of either a titrating or 'block and replace' regime in preventing relapse. Many patients did not have their thyroid antibodies retested prior to withdrawing anti-thyroid medications. The importance of doing this and using it as a guide when considering withdrawal of treatment will be publicised within the team. A further audit will be performed in due course to see whether this has been successfully implemented and has influenced the rate of relapse.

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AEP968

Evaluation of 24-hour electrocardiogram parameters in patients with graves disease before and after anti-thyroid therapy

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Background
We aimed prospectively investigate the laboratory and electrocardiographic parameters (hearth rate, QRS, QT, QTc, Tpe, Tpe/QTc, arrhythmia prevalance) in patients with graves disease before and after antithyroid therapy.
Methods
71 patients (48 female, 23 male), age between 18–50 (mean±S.D.: 36.48±12.20) with GD were included into the study. Patients treated with antithyroid therapy (thionamids and/or surgical therapy) to maintain euthyroid status. Patients were examined in terms of electrocardiographic parameters before and after the treatment.
Results
Mean TSH, free thyroxin (fT_4) and tri-iodothyrionine (fT_3) levels of all patients were 0.005±0.21, 3.27±1.81, 11.42±7.44, respectively. While 9 patients (group 2) underwent surgical therapy, had suspicious of malignant nodule or large goiter and unresponsiveness to medical treatment; the other patients (n=62, group 1) were treated with medical therapy. Patients with surgical therapy had more increased serum fT4 ($P=0.045$), anti-thyroglobulin value ($P=0.018$) and more severe graves orbitopathy ($n=0.051$) before treatment when compared to medical therapy group. Baseline Tpe duration and baseline Tpe/QTc ratio and frequency of supraventricular ectopic beats were found to be significantly higher in group 2 when compared to group 1 ($P=0.00$, $P=0.005$). Otherwise baseline mean heart rate, QRS duration, QTc values of both groups were similar. Although the patients became their euthyroid status, group 2 patients had still suffered from more sustained supraventricular ectopics beats than group 1.
Conclusions
Distinct from medical treatment group, surgical treatment group with euthyroidism at least 3 months had still suffered from an arrhythmia (Tpe, Tpe/QTc, supraventricular and ventricular ectopic beats).

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AEP969

Reducing unnecessary thyroid fine needle aspiration using ACR-TIRADS system

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Introduction
Thyroid ultrasound is the main technique to study this gland's pathology. ACR TI-RADS system evaluates the malignancy risk in thyroid nodules according to their sonographic features and stablishes the size in which to perform fine needle aspiration (FNA) for its cytological study. Nodules diagnosed as Bethesda category 4 (B4) means are follicular neoplasms or suspicious for follicular neoplasms.
Aim
Determine the pathology diagnosis of B4 nodules and study associations among malignancy and ACR-TIRADS sonographic features.
Material and methods
Retrospective study of thyroid nodules classified as B4 in FNA in our hospital between 2012 and 2018. Statistical analysis: SPSS v.22.0 (Student's t-test to compare means and Squared Chi/Fisher to proportions).
Results
162 nodules classified as B4 in FNA. Mean age: 54.07±14.62 years. 75.3% Women. 2.6% nodules stratified as ACR TI-RADS 2 with mean longest

diameter (MLD) of 35.25 cm. 23.9% ACR TI-RADS 3 with MLD of 31.94 mm, 66.5% ACR TI-RADS 4 with MLD of 30.19 mm and 7.1% ACR TI-RADS 5 with a MLD of 29.09 mm.

Composition		Echogenicity		Shape		Margin		Echogenic Foci	
Feature	%	Feature	%	Fea-ture	%	Feature	%	Feature	%
Cystic or almost completely cystic	**0**	Hypere-choic or isoechoic	**24.5**	Wider than tall	**94.2**	Smooth	**93.5**	None or large comet-tail artifacts	**87.1**
Spongiform	**0**	Hypoechoic	**71.0**	Taller than wide	**5.8**	Lobulated or irregular	**6.5**	Macro-calcifications	**5.8**
Mixed	**3.9**	Very hipoechoic	**4.5**			Extra-thyroidal extension	**0%**	Peripheral-calcifications	**1.3**
Solid or almost completely solid	**96.1**							Punctate echogenic foci	**5.8**

29 (17.8%) nodules met standard malignancy criteria: 15 papillary thyroid carcinomas, 12 follicular thyroid carcinomas and 2 medullary carcinomas. If ACR TI-RADS had been strictly followed, 25.2% of FNA could have been avoided. Among nodules without FNA indication, 3 were malignant (2 papillary and 1 follicular carcinoma). Of those with FNA indication 24.5% were malignant. In our cohort, ACR TI-RADS system was of 88.8% (CI 95% 1.08–0.77) and specificity of 30.2% (CI 95% 0.38–0.21). Positive predictive value was 24% and negative predictive valuewas 91%.

Conclusions

FNA performed could have been reduced in our cohort if the decision had been taken upon the strict application of ACR TI-RADS system. Given the low rate of false negative nodules, ACR-TIRADS constitutes a good screening method to determine which nodules should undergo FNA.

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AEP970

Falsely elevated FT4 measurements with an electrochemiluminescent assay

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Introduction

Recently Roche Diagnostics (Rotkreuz, Switzerland) introduced the third generation of its Elecsys free thyroxine (FT4 iii) assay (in Greece from February 2019 onwards). The new assay is considered to have reduced biotin interference compared to its previous version (Ft4 ii). Kits of the FT4 ii assay are still available (and valid) according to the manufacturer's expiration date. Using the FT4 ii assay per the manufacturer's instructions we noticed FT4 results that were incongruent both with thyrotropin (TSH) and subsequently with free triiodothyronine (FT3) levels and the clinical presentation of patients.

Aim – Methods – Results

Evaluation with a Bland-Altman plot of FT4 ii results vs the FT4 iii assay's results in 40 consecutive and unselected subjects showed few outliers (Figure 1). However, the results of twice as many patients (22/40 with FT4 ii vs 10/40 patients with FT4 iii) were in the hyperthyroid range (Mcnemar's $P=0.005$). From the subjects' history-taking, interference by biotin (or by other substances) was ruled out. Finally the problem was traced to the provided assay's calibration. This was communicated for assessment to the manufacturer.

Discussion

Knowledge of this is useful, particularly in the quest for recalibration of assays against reference measurement procedures[1,2].

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AEP971

Role of thyroid ultrasonography in egyptian patients with hashimoto`s thyroiditis; a pilot study

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Background

Hashimoto's thyroiditis (HT) is considered the most common autoimmune disease and the predominant cause of hypothyroidism in iodine sufficient countries. HT may appear clinically in approximately 0.1–2% of the population.

Aim

The study in hand aimed at assessing the role of thyroid ultrasonography in the diagnosis of HT patients discriminating them from other causes of hypothyroidism. A scoring system of sonographic findings was aimed to be used side by side with the auto antibodies routinely used for diagnosis.

Subjects

The current study included 160 subjects with manifestations of hypothyroidism,who attended Cairo University, Kasr Al-Ainy Outpatient Endocrinology Clinic,112 patients with HT and 48 hypothyroid non-Hashimoto's controls.

Methods

All included patients were subjected to full history taking, clinical and local thyroid examination, BMI calculation, thyroid ultrasound examination (US) and a panel of assays (TSH, f.T3, f.T4, anti-TPO Ab, anti-TG Ab, calcium, alkaline phosphatase and phosphate). Regarding thyroid US scanning, the number of US findings (thyroid volume, heterogeneity, nodularity and vascularity) were counted for each studied patient. A score was given to each patient ranging from 0 (no finding) to 4 findings. Thyroid antibodies were assayed using ELISA.

Results

112 subjects were considered as HT (with anti-TPO Ab levels >75 IU/ml and/or anti-TG Ab > 110 IU/ml). 48 subjects were included as control group (withnegativeanti-TPO Ab and anti-TG Ab; <20 IU/ml and <90 IU/ml respectively). A statistically significant increase in total thyroid volume was observed in HT patients ($P=0.002$).A cutoff volume ≥4.8 ml was found discriminative with specificity (95% CL) of 60.4 (45.3–74.2)% and sensitivity of 65.2 (55.6–73.9)%. However, the remaining thyroid US features were statistically insignificant. A discriminatory cutoff for the scoring system was studied to differentiateHT patients from control group based on the number of their US findings. No significant difference was found between both groups, whether 0–1 vs 2–4 scores; ($P=0.422$), or 0 vs 1–4 ($P=0.104$).

Conclusion

All positive thyroid ultrasound findings cannot discriminate between HT and other hypothyroid non-Hashimoto's patients except thyroid volume. No scoring system based on US findings can be adopted for diagnosis of HT. However, a thyroid volume at a cutoff of 4.8 ml can be an added value to the laboratory findings to discriminate between HT and control group with specificity 60.4% and sensitivity 65.2%.

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AEP972

Determinants of the health related quality of life of adult filipinos with differentiated thyroid cancer

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Objective

This study aims to investigate clinical and demographic variables associated with HRQoL as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Questionnaire (EORTC QLQ C30) Tagalog and the Thyroid Cancer-Specific Quality of Life Questionnaire (TCS QLQ) Tagalog.

Methodology

234 adult Filipinos with histopathologic-confirmed diagnosis of DTCafter thyroidectomy with or without radioactive iodine were recruited and asked

to answerthe EORTC QLQ-C30 and TCS QLQ Tagalog versions. Demographics and clinical data were collected. Factors influencing HRQoL scales were analyzed using multivariate linear and logistic regression.
Results
Adult Filipinos with DTC showed a high a level of functionality (EORTC QLQ C-C30 functional and global domain score range 72–84) and low level of thyroid specific complaints like neck pain and hoarseness (TCS QLQ Tagalog score range 1.6–2.06). Additionally, they report a moderate level of fear about cancer recurrence and repeat treatments. Multivariate analysis identified Stage IV disease, neck dissection, comorbidity, hypothyroidism, and middle-income class being associated with lower quality of life scores in the two questionnaires.
Conclusion
Adult Filipinos with DTC following up after thyroidectomy have good HRQoL overall. Socio-economic status and a few clinical and treatment-related factors negatively influenced HRQoL in this population.

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AEP973

Diagnostic value of Bethesda system for reporting thyroid cytopathology in patients with prior thyroid surgery

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Background
Fine needle aspiration biopsy (FNAB) and Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) have proven to be the most valuable diagnostic procedure for preoperative discrimination of benign and malignant thyroid nodules. Thyroid surgery may cause regional scarring and some degree of fibrotic process which may result in problems when collecting FNAB samples and evaluating the cellular abnormalities. In this study, we aimed to determine whether the Bethesda classification system in thyroid nodules is reliable in patients with a history of thyroid surgery.
Methods
We retrospectively examined outcomes of 130 patients with 260 nodules who underwent a thyroidectomy for recurrent goiter (Group 1) and compared them with 2821 patients with 5890 thyroid nodules who underwent first thyroidectomy (Group 2) in our center between 2007 and 2014.
Result
Malignancy rate was significantly lower in group B (24 (18.5%) patients) compared to group A (911 (32.3%) patients) ($P=0.016$). The most frequent operation indications in group A may explain the hight rate ofmalignancy in this group, that were giant nodule and suspicious cytology results in group B and group A respectively ($P=0.001$). Hypothyroidism was significantly higher in group B and result by a hight ratio of gaint nodules ($P=0.001$). Although a relationship between giant nodule and higher malignancy rate was reported in previous studies, we did not find a correlation between giant nodules and malignancy rate of patient in group B. Diagnostic value of Bethesda was determined in patients with primary and reoperative thyroid surgery. Benign cytology was considered negative and suspicious for malignancy and malignant cytologies were considered positive. sensitivity, specifity, PPV, NPV and accuracy of Bethesda classification in patients with primary thyroid surgery were 74.50%, 98.18%, 83.38%, 96.92% and 95.60%, respectively. In patients with reoperative thyroid surgery, sensitivity was 62.50%, specifity was 98.91%, PPV was 71.43%, NPV was 93.38% and accuracy was 97.39%.

Table 1 Diagnostic value of Bethesda classification in patients who underwent primary and reoperative thyroid surgery.

	Primary		Reoperative	
	a ($n=3710$)	b ($n=3814$)	a ($n=192$)	b ($n=199$)
Sensitivity	74.50%	76.37%	62.50%	66.66%
Specifity	98.18%	96.09%	98.91%	95.79%
Positive predictive value	83.38%	71.61%	71.43%	42.86%
Negative predictive value	96.92%	96.92%	98.38%	98.38%
False positive	16.62%	28.38%	28.5%	57.14%
False negative	3.07%	3.07%	1.62%	1.62%
Accuracy	95.60%	93.83%	97.39%	94.47%

Conclusion
FNAB is known to be the most accurate and cost-effective method that provides avoidance of unnecessary surgery in 25% of patients with benign thyroid disease. A lower frequency of malignancy was observed in patients/nodules with reoperative thyroid surgery compared to patients/nodules with primary thyroid surgery in this surgical series. Sensitivity and PPV of Bethesda were affected negatively by previous thyroid surgery. This might be considered in these patients while deciding for a recurrent surgery which has a higher risk of complications.

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AEP974

Humoral changes during resolution of short term severe hypothyroidism

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Introduction
Significant hyponatremia may evolve in hypothyroidism, when however, elevated ADH levels have not been consistently demonstrated. On the other hand, it was shown that thyroid hormone substitution suppresses ADH, and its surrogate marker copeptin secretion. The aim of our present study was to investigate the possible humoral changes in a special model of resolution of short term severe hypothyroidism in differentiated thyroid cancer (DTC) patients.
Patients
In 39 DTC patients (11 men, 28 women, mean age 50.28 ± 14.90 ys) in whom DTC was not advanced (ECOG: 0) blood samples were obtained on the day of radioiodine therapy and 10–12 weeks after thyroxine supplementation.
Results
Serum sodium (140.8 ± 2.6 vs 142.3 ± 1.8; $P=0.002$), chloride (100.8 ± 3.4 vs 102.5 ± 2.6; $P=0.012$), potassium (4.3 ± 0.4 vs 4.4 ± 0.3; $P=0.025$), eGFR (77.0 [61.0–90.0] vs 90.0 [72.0–90.0]; $P<0.001$), NT-proBNP (36.8 [20.6–73.7] vs 69.6 [37.4–194.9]; $P<0.001$), ACTH (11.9 [10.0–16.0] vs 16.4 [12.2–22.5]; $P=0.001$) and renin activity (0.7 [0.4–1.6] vs 1.6 [0.9–2.9]; $P=0.003$) were lower during hypothyroidism, while cortisol, aldosterone and copeptin were similar. Of the investigated parameters copeptin showed positive association with sodium in univariate ($r=0.226$; $P=0.046$) and to TSH in multivariate correlations (R square = 0.123; $P=0.001$). Serum sodium levels had a variance of 5.47 mmol/l and, beside copeptin, were associated to concentrations of TSH ($r=-0.321$; $P=0.004$), ACTH ($r=0.349$; $P=0.002$) and cortisol ($r=0.225$; $P=0.047$). However, none of them were independent determinants of serum sodium levels in multiple regression analyses.
Conclusion
According to our investigations, TSH is an independent predictor of copeptin level. The serum sodium level is significantly lower in short term severe hypothyroidism, but this cannot be appropriately explained by the investigated humoral parameters.

Keywords: TSH, DTC, hypothyroidism, hyponatraemia, copeptin.
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AEP975

The concordance between ultrasonographic EU-TIRADS and cytologic bethesda criteria of thyroid nodules

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Objective
The aim of this study was to evaluate the capability of the thyroid nodule ultrasonography criteria of the European Thyroid Imaging and Reporting Data System (EU-TIRADS) to predict fine needle aspiration cytology results categorised by The Bethesda system.
Methods
A retrospective analysis was made out of 310 cases of an outpatient clinic over a period of 1 year (2018.03–2019.03). We compared single-specialist-performed thyroid nodule ultrasonography findings categorised by EU-TIRADS to the cytopathology results of fine needle aspiration that we assigned to specific Bethesda categories. The thyroid nodules were divided into benign with ultrasonography findings of EU-TIRADS 2–3 and cytopathology of Bethesda 2 and malignant with EU-TIRADS 5 and Bethesda 5–6. Statistical analysis was performed using SPSS 23.0.
Results
We assembled cases of 310 people of which 279 (90%) were female and 31 (10%) were male. 4 patients were assigned to benign (EU-TIRADS 2), 191 low-risk (EU-TIRADS 3), 68 intermediate-risk (EU-TIRADS 4) and 47 high-risk (EU-TIRADS 5) category on ultrasonography. Overall concordance rate of EU-TIRADS and fine needle aspiration findings was 75.48%. The probability of benign pathocytology result in EU-TIRADS 2, 3, 4 and 5 was 100%, 95.3%, 72.1% and 38.3% respectively. At the same time the risk of finding a malignant cytology result was 0% with EU-TIRADS 2, 1.1% with EU-TIRADS 3, 13.2% with EU-TIRADS 4 and 38.3% with EU-TIRADS 5. Specificity and sensitivity was 91.2% and 90% accordingly. The positive predictive value was 50% and the negative predictive value was 98.9%. The association between EU-TIRADS and fine needle aspiration findings was good according to the ROC curve and the area under the curve with 0.879.
Conclusions
The categories of thyroid nodule malignancy risk in EU-TIRADS have a good correspondance to Bethesda cytopathologic categories. Concordance between the benign ultrasonography and cytology criteria is more significant compared to malignant. With every higher category of EU-TIRADS the probability of malignant cytology result increases.
Keywords: fine-needle aspiration biopsy, The Bethesda System, EU-TIRADS, thyroid nodule.

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AEP976

Association of a medullary thyroid carcinoma, a papillary thyroid carcinoma and a renal carcinoma: Towards a new neoplastic syndrome?

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Introduction
Multiple primary cancers are a rare entity; however their incidence is increasing due to advances in diagnostic methods and surveillance strategies. The coexistence in the same patient of several primary malignant tumors has been described in the literature with a frequency varying from 5.5% to 8.5%. The aim of this observation is to report a case associating 3 neoplasias:medullary thyroid carcinoma (MTC), papillary thyroid carcinoma (PTC) and a renal carcinoma.
Case report
A 49-year-old male patient consulted for a compressive thyroid goiter. A Fine-needle aspiration biopsywas conducted, revealing a MTC. A laryngectomy with total thyroidectomy, bilateral mediastino-recurrent lymph node dissectionwith the installation of a tracheostomy was performed. The pathology study showed 2 synchronous thyroid tumors: medullary and papillary thyroid carcinoma. MTC invaded the trachea with lymph node metastases, classified as pT4a N1b, as for PTC, it was 1.8 cm in length with lymph node metastases, classifiedas pT2 N1b. The extension assessment identified costal bone metastases and a left renal tumor, which turned out to be a renal tubulo-papillary carcinoma at histological examination. For the PTC, the patient was treated with 200 mCi of iodine-131 with negativation of thyroglobulins. However, the MTC evolution was not the same; the basal serum level of calcitonin has increased, with the progression of bone metastases. As for the family history, there was no record of any thyroid or kidney tumors. The final treatment of the patient was mainly palliative.
Conclusion
The coexistence of several neoplasias is rare, and poses major diagnostic and therapeutic problems, and it requires multidisciplinary management. The role of genetic study is essential in this area to codify these different diseases into a syndromic approach.

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AEP977

Risk factors of disease recurrence among Filipino patients with low-risk papillary thyroid carcinoma in manila doctors hospital: A retrospective cohort study

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Background
New emerging studies demonstrated that mortality from thyroid cancer and disease recurrence was significantly higher among Filipinos compared with other ethnic groups. However, exact mechanisms which could explain these findings among Filipino patients remain to be poorly understood. The risk factors associated with disease recurrence among adult Filipino patients with low-risk papillary thyroid cancer in Manila Doctors Hospital was assessed in this study.
Methods
This was a retrospective cohort study which included 39 Filipino patients diagnosed with low-risk papillary thyroid carcinoma treated at Manila Doctors Hospital. Demographic characteristics, pertinent clinical data and physical findings were extracted from the medical charts. Clinical and biochemical parameters were analyzed to determine their association with disease recurrence using Multivariate regression analysis. Cox regression analysis was done to identify significant risk factors for disease recurrence.
Results
Out of the 39 patients included in the study, 8 patients had disease recurrence (20.5%). Anti-Tg antibody level of ≤50 u/ml demonstrated significant protection against the development of disease recurrence (HR: 0.13, *P* value: 0.015). Tumor diameter of more than 4 cm (HR 34.10, *P* value 0.012) was significantly associated with disease recurrence.
Conclusion
Our study showed that the incidence of disease recurrence was 20.5%, and anti-Tg antibody level of ≤ 50 u/ml and tumor diameter of more than 4 cm demonstrated significant protection against disease recurrence and significant association with disease recurrence, respectively. The identification of risk factors for disease recurrence may help guide us in providing specific treatments tailored for low-risk PTC Filipino patients and closer follow up interval to further improve the outcome.
Keywords: disease recurrence, low-risk papillary thyroid carcinoma, Filipino.

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AEP978

Large 'forgotten goiter' in the thoracic cavity – a case report

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Introduction
'Forgotten goiter' is defined as a mediastinal thyroid mass discovered after total thyroidectomy. It is a rare clinical finding, usually asymptomatic.
Case report
88-years old woman was admitted to the Endocrinology Department with a suspicion of the retrosternal goiter. In her medical history there was

thyroidectomy performed 16 years before because of multinodular goiter and she had recurrent lower respiratory tract infections in the last few months. She did not present any symptoms of impaired hormonal secretion, however thyroid function tests showed subclinical hyperthyroidism. Chest X-ray and then CT examination revealed in the thoracic cavity a mass reaching to the diaphragm and connected with the thyroid. Technetium 99 m pertechnetate scans confirmed that as a thyroid mass. Taking into consideration patient's age and contraindications to the surgery, the decision about treatment with radioactive iodine was made and patient received 20 mCi I-131. Three months after therapy patient was euthyroid, however a year after recurrence of a subclinical hyperthyroidism was found. Patient was treated with radioiodine in a dose of 20 mCi again. 15 months after the second radioiodine administration, patient remained euthyroid and a volume of the goiter has decreased.
Conclusion
In the literature there are described case reports of patients diagnosed with 'forgotten goiters', but the treatment of choice was surgery, what was contraindicated in our patient. What is more, the goiter of a size as the one diagnosed in reported patient is extremely rarely found.

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AEP979

Primary Thyroid Teratoma – a rare diagnosis

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Introduction
A teratoma is a rare type of tumor deriving from the germ layer cells (ectoderm, mesoderm and endoderm), typically benign, more frequent in infants. Adult onset teratomas are most commonly gonadal cell tumors. Extra-gonadal teratomas generally affect the midline, most frequently anterior mediastinum, retroperitoneum, pineal and suprasellar area. Head and neck teratomas are an extremely rare entity and represent only 0.47–6% of all cases.
Case report
Female patient, 70 years old, no relevant personal or familial history. Patient is followed in Endocrinology outpatient care due to to an heterogeneous, predominantly hypoechoic nodule, 25 mm in length, located in the right thyroid lobe. Given the nodule description the patient underwent a fine needle aspiration. The result suggested a follicular lesion of undetermined significance/atypia of undetermined significance. The fine need aspiration was repeated with an inconclusive result. The third fine needle aspiration revealed the presence of a proteinaceous, amorphous tissue, with numerous vacuoles and squamous cells compatible with a branchial cyst. Due to the appearance of compressive symptoms a CT cervical scan was ordered. The image exam showed the presence of a nodular lesion, $19 \times 29 \times 25$ mm of well defined limits, heterogenous, with soft tissue, macroscopic fat and calcium fragments suggestive of a teratoma, causing tracheal and esophageal deviation, with no associated cervical adenomegalies. The patient was subjected to a right thyroid lobectomy. The pathological analysis revealed a pseudo-encapsulated nodule, occupying nearly all of the right thyroid lobe, with 30 mm of long axis, compatible with a cystic mature trigerminative teratoma, composed exclusively by well differentiated elements (grade 0).
Discussion
Thyroid teratomas represent less than 0.1% of all primary thyroid tumors. These lesions typically present as cystic or mixed lesions and the cytological result might be inconclusive. Despite being more frequent in children, teratomas do not spare any age group.

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AEP980

Secondary intrathyroid localization of a pulmonary papillary carcinoma

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Introduction
Intrathyroid metastases are rare (less than 1% of thyroid cancers). They can be synchronous or metachronous. The origin of primary cancer is variable; the kidney, lung, stomach and breast being the most described sites. Through this case, we describe the diagnostic difficulties that the pathologist may encounter in the identification of these metastases.
Materials and methods
We report a case of intrathyroid metastasis of a pulmonary papillary micro carcinoma.
Results
She was a 73 year old patient with no particular pathological history, who presented a right spinal swelling appeared 2 months ago and gradually increasing in size. She had dyspnea and swallowing discomfort without signs of dysthyroidism. Physical examination found a free thyroid gland as well as lymph nodes. Cervical ultrasound showed multiple cervical jugulo-carotid and subdigastric lymphadenopathy associated with an isthmic thyroid nodule of 8 mm. The lymph node biopsy concluded that there was lymph node metastasis from papillary carcinoma. The patient had a total thyroidectomy with a right functional lymph node dissection and bilateral recurrent laryngeal nerve lymph node dissection with favorable operative suites. The diagnosis of lymph node metastasis from a pulmonary papillary micro-carcinoma was made on final histological examination. The thoracic CT made subsequently objectified multiple pulmonary nodules. Fibroscopy with biopsy confirmed the diagnosis of branchic adenocarcinoma in its micro papillary form. The patient had 3 chemotherapy courses with good progress.
Conclusion
The frequency of intrathyroid metastases is probably underestimated. The examination of the thyroid and a cytopuncture at the slightest doubt seems logical. Thyroidectomy is rarely indicated. The prognosis depends on the primitive.

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AEP981

Rhabdomyolysis from severe hypothyroidism – A case report

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Introduction
Hypothyroidism can cause various degrees of muscular disorders. It can lead to symptoms such as myalgia, weakness, fatigue and in rare cases to extreme muscular damage such as rhabdomyolysis, a potential life-threatening complication. We present the case of a 53 years old patient with acute renal failure due to rhabdomyolysis from severe hypothyroidism.
Case description
The patient, a male from Albania was first admitted to the Emergency Room with complaints of severe weakness and profuse sweating. He was hospitalised in the Department of Nephrology with Acute Renal Failure from Rhabdomyolysis probably from lipid lowering medications. The patient had a short history of treatment with Statins. He was discharged after a week with moderate elevated creatine kinase level (CK 2000 UI/l) and the treatment with Statins was interrupted. The patient was re hospitalised, two weeks after being discharged with the same symptoms and elevated muscular enzymes. Blood tests were as followed: Urea 34 mg/dl, Creatinine 1.7 mg/dl, LDH 725 U/l, CK 5130 U/l. At the moment, he was not taking any lipid lowering medication and he did not have any history of extreme exercise. He had a history of several months of stiffness, feeling cold, swelling and inexplicable weight gain. Because of these clinical manifestation, a level of thyroid stimulus hormone (TSH) and anti-thyroid peroxidase antibodies (anti – TPO) were taken and they both were very high [TSH > 75 U/ml (0.4–4 U/ml) and anti TPO–1050 U/ml (<60 U/ml)]. The diagnose of hypothyroidism was later confirmed with ultrasound of the thyroid gland where it was evident a heterogeneous structure, an aspect favouring Hashimoto Thyroiditis. The patient was started therapy with Levothyroxine and the level of muscular enzymes declined, as well as his symptoms.
Conclusion
Hypothyroidism is a rare but potential cause of rhabdomyolysis when other risk factors are excluded. In order to prevent complications from rhabdomyolysis such as acute renal failure, we should always consider thyroid gland function when elevated muscular enzymes are present alongside symptoms of hypothyroidism.

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AEP982

Exophtalmos in a hyperthyroid patient – it's not always Graves ophthalmopathy

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Background
Hyperthyroidismcan be associated withorbitopathy that manifests as exophtalmos due to orbital tissue inflammation. Usually the diagnosis is straight forward when an autoimmune thyroid disorder is present, but conditions mimicking Graves orbitopathy can pose a diagnostic challenge.
Case report
We report the case of a 51 year old caucasian woman who was referred to our clinic with asymmetrical exophtalmos in november 2019. The patient stated that she first experienced the right eyeball protrusion after a difficult labour in 1999 but with no ophthalmologic examination until 2019 when she noticed a sudden decrease in the right eye visual acuity following, probably coincidental, blunt ocular trauma. Ophthalmological exam and visual field testing showed almost complete loss of vision in the right eye. She was reffered for endocrinological exam with asymmetrical exophtalmos (ocular protrusion of 24 mm in the right eye and 18 mm in the left eye), upper lid retraction, fine tremor of the hands and a history of palpitations and heat intolerance. Lab results revealed mild hyperthyroidism: TSH < 0.004 µIU/ml (0.4–4.0), FT_4 = 1.79 ng/dl (0.89–1.76), TT_3 = 123 ng/dl (72–179), the lack of thyroid autoimmunity: TPOAb < 10 IU, antithyroglobulin antibodies = 10 IU/ml (10–115), TRAb = 0.765 IU/l (0–1.75).The other blood tests were unremarkable, except an inflammatory syndrome, with a CRP of 34 mg/l (0.2–11). Thyroid ultrasound diagnosed a multinodular goiter. Magnetic resonance imaging and magnetic resonance angiography of the brain and orbital MRI were compatible with optic neuritis of the right eye and showed normal dimensions of the extraocular muscles: right eye – medial rectus = 3.6 mm, lateral rectus = 3.6 mm, superior rectus = 4 mm, inferior rectus = 4.7 mm; left eye – medial rectus = 3.2 mm, lateral rectus = 4.7 mm, superior rectus = 3.3 mm, inferior rectus = 5.3 mm. Moreover, orbital fat was in normal limits. Multidisciplinary team decided rheumatological and neurological check-up for differential diagnosis and a trial of salvage treatment with intravenous methylprednisolone 250 mg weekly for 6 weeks. Interestingly, follow-up perimetry test after 3 weeks showed significant improvement in the visual field of the right eye.
Conclusions
Diagnosis and treatment of orbitopathy in a hyperthyroid patient with no autoimmune thyroid disease proves to be an arduous process. Our patient's visual field improved dramatically after systemic methylprednisolone administration even though she did not meet the diagnostic criteria for Graves orbitopathy. In such instances a multidisciplinary effort is required in order to identify the underlying cause and provide adequate care.

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AEP983

Hurthle cell carcinoma – A case report

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Introduction
Hurthle cell carcinoma was considered to be a variant of follicular thyroid cancer. However, recent clinical and molecular studies clearly indicate that Hurthle cell cancer is a distinct tumor type. Histologically, it is characterized by the presence of a cell population of 'oncocytes', mostly eosinophilic oxyphilic cells and abundant cytoplasm,closely packed mitochondria, and round oval nuclei with prominent nucleoli. Unlike follicular thyroid cancer, Hurthle cell cancer has more of propensity to to spread to cervical lymph nodes. Hurthle cell cancer metastatic foci are often radioactive iodine refractory. This type of carcinoma accounts for only about 3–10% of all differentiated thyroid cancers.
Case
A 51-year-old women was presented in our policlinic with a visibile mass on the neck. She complains about difficulty swallowing and hoarseness. On physical examination we detect enlargement and stiffness of the right lobe ofthyroid gland. Thyroid ultrasonography revealed a 3 cm hypoechoic nodule with cystic degeneration on the right lobe. The left lobe and istmus were normal. Thyroid hormone tests showed normal thyroid-stimulating hormone (TSH) 2.28 uIU/ml (reference value 0.3–4.5uIU/ml), normal FT4 12.7 pg/ml (normal range 8.9–17.2 pg/ml) and normal FT3 2.1 pg/ml (normal range 1.21–4.18 pg/ml). Thyroid scintigraphy (technetium(TC)-99 m) showed enlarged right lobe,and acold nodule in the lower part of this lobe. The left lobe was non enlarged, with low homogeneous fixation, isthmusi non-homogenous. Thetotal uptake was in range. A Fine-needle aspiration (FNA) biopsy was performed and showed suspected neoplasia with Hurthle cells. The patient underwent surgical intervention. Total thyroidectomy was performed, No local lymph nodes resection. The postoperative biopsy conclude:Proliferative process of oxyphil carcinoma type. Further immunohistochemial test confirmatethe diagnosis. There were no evidence of invasion of the Hurthle cell cancer (metastasis) beyond the thyroid gland, so substitutive hormone therapy was started. Radioactive Iodine Treatment (RAI) was not performed. Periodic follow-ups every 6-months are done with ultrasound examination and hormone levels. She is free of metastases so far.
Conclusion
Hurthle cell carcinoma may be associated with poor prognosis than follicular cancer, related with the poor affinity for taking radioiodine. Hurthle cells has been shown to have an increased recurrence in local lymph nodes. Our case was a middle aged woman with a cold nodule nearly 3 cm, with no evidence of lymph node involvement.
Keywords: hurthle cell carcinoma, oxyphilic carcinoma, lymph nodes, radioactive iodine.
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AEP984

The flight of the thyroid- the butterfly effect

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Introduction
Dual nivolumab and ipilimumab immunotherapy has the potential of causing an immune-mediated thyrotoxicosis, precipitating thyroid storm.
Case details
A 62-year-old Caucasian woman with a history of Lung Carcinoma (Non small Cell Lung Carcinoma) presented to the emergency department, with a 3-day history of intractable nausea, severe headache, vomiting and anxiety. She had been initiated on dual nivolumab and ipilimumab therapy 6 weeks prior and received two courses of therapy thus far. Her last dose was 10 days prior to presentation.
Past medical history
a. Hypertension.
b. Depression.
c. Osteoarthritis.
d. Newly diagnosed Lung Carcinoma (NSCLC).
Investigations
- CXR-No evidence of consolidation/Pulmonary Oedema.
- Blood Cultures-Negative.
- Urine dip-Negative.
- Bloods- Revealed Leucocytosis, elevated CRP levels.
- CT Head-Nil evidence of Intracranial haemorrhage/SOL.
- Lumbar puncture-was performed and resultant Gram stain, culture, cell count, protein and glucose were all normal.
- TSH- <0.001 (0.4–4.0 mU/l).
- FT4–36.2 pmol/l (9.0–25.0 pmol/l).
- FT3–9.8 pmol/l (3.5–7.8 pmol/l).
- Thyroid peroxidase and thyroid stimulating immunoglobulin levels were within normal range.
- Scoring systems- Burch- Wartofsky Score- 55 – indicative of Thyroid storm.

Management
- Beta-blockers: propranolol 1–2 mg intravenously or 40–80 mg per os every 8 h is the drug of choice because, on the one hand, contrasts the increased binding of catecholamine to beta-adrenergic receptors, on the other hand, reduces the T4 to T3 peripheral deiodination.
- Thyrostatics: methimazole 15–20 mg every 6 h or propylthiouracil with a loading dose of 500–1000 mg followed by 250 mg every 4 h. It should be mentioned that rectal administration of both methimazole and propylthyouracyle is allowed, at a dose of 400–600 mg every 6 h and 20–40 mg every 8–6 h, respectively.

- Large iodine amount: Lugol solution or saturated potassium iodide solution (or sodium iodide 500–1000 mg daily intravenously inhibits thyroid hormone leakage by the thyroid gland. Iodine should be administered not sooner than 1 h after anti-thyroid drug administration.
- Glucocorticoids: hydrocortisone 100 mg intravenously every 6–8 h reduces the T4 to T3 peripheral deiodination

Summary

- Thyroid function tests and thyroid symptoms should be monitored in patients with undergoing nivolumab and ipilimumab immunotherapy
- Prompt treatment of thyroid storm is potentially life-saving. Close monitoring in an inpatient setting in addition to treatment with β-blockers, antithyroid agents, steroids and bile sequestering therapies are recommended.
- Thyroid storm is a clinical diagnosis, usage of Scoring tools-Burch-Wartofsky score and the Japanese Thyroid Association Scoring System recommended.
- Thyroid function tests and thyroid symptoms should be monitored in patients with undergoing nivolumab and ipilimumab immunotherapy
- Prompt treatment of thyroid storm is potentially life-saving. Close monitoring in an inpatient setting in addition to treatment with β-blockers, antithyroid agents, steroids and bile sequestering therapies are recommended.
- Thyroid storm is a clinical diagnosis, usage of Scoring tools-Burch-Wartofsky score and the Japanese Thyroid Association Scoring System recommended.

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AEP985

A correlation study between histological results and thyroid ultrasound findings. The EU TI-RADS classification

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Introduction
The management of patients with nodular goiter and thyroid neoplasms is one of the most important problems in modern thyroidology. There are several classifications based on thyroid ultrasound for selecting suspected malignant thyroid nodules. The Thyroid Imaging Reporting and Data System (TI-RADS) classification is an easy to apply for thyroid lesions, which might be helpful in clinical practice for the initial assessment of the thyroid lesion risk of malignancy.
Material and methods
A retrospective study of all patients who underwent thyroid surgery at the ENT department of Tahar Sfar Hospital in Tunisia (*n*= 108) from January 2013 to December 2017. After surgery, histological results were correlated to the ultrasound findings reported.
Results
The mean age of our patients was 46 years. A clear predominance of women was found (94% of the cases). 17% of the cases were diagnosed with thyroid cancer and 83% of the cases with benign disease. Correlation of histological results with preoperative ultrasound reports showed an initial sensitivity of 95%, a specifity of 82% with positive and negative predictive values of 53% and 98%.
Conclusion
The TIRADS score is an interesting tool in the detection of malignant thyroid nodules, thus avoiding excessive surgical indications. The use of the TI-RADS scale would also allow for an adequate selection of patients amenable to fine needle aspiration of the nodule

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AEP986

A retrospective 5-year follow-up study on the outcomes of radiofrequency ablation for the treatment of benign thyroid nodules

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Background
During the last decade, radiofrequency ablation (RFA) has emerged as a reliable alternative to surgery for the treatment of benign symptomatic thyroid nodules in terms of effectiveness and safety.
Aim
The aim of this study were: (*i*) to evaluate the long-term efficacy (5 years) of RFA for the treatment of benign thyroid nodules, in terms oftechnical success and nodule regrowth, and (*ii*) to identify the predictive factors of technical failure and nodule regrowth.
Materials and methods
79 patients who underwent RFA for benign symptomatic thyroid nodules were included in this observational retrospective study. All the patients were followed up yearly for 5 years after the procedure. Regrowth was defined as a nodule volume increase greater than 50% as compared to the previously reported smallest volume after the procedure.
Results
Our analyses show that RFA led to a nodule volume reduction of 72% after one year and 76% after five years from the procedure. The technical success rate was 91%, while regrowth rate was 21.4% in 5 years. Nevertheless, in the majority of cases regrowth was not associated with symptom recurrence. Overall, only 12.7% of the patients were retreated after 5 years. In particular, 5 patients underwent surgery (all the nodules resulted benign at the final pathology), while 5 patients underwent a further session of RFA. The nodule volume reduction after one year from the second procedure was still 67%. Our results show that sex was a predictive factor of technical failure; while sex, age (with an inverse correlation), symptoms, and technical failure were predictive of regrowth.
Conclusions
RFA is effective for the treatment of symptomatic benign thyroid nodules. Overall, RFA is associated with a low rate of failures and regrowths requiring further treatments. Neverheless, if a second procedure is needed, it will further decrease nodule volume by 67%. Furthermore, our data suggest that patients should be followed up after the procedure.

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AEP987

Is there a place for Thyroid Scintigraphy with Technetium 99 m in the exploration of congenital hypothyroidism in the absence of Iode 123

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Introduction
With a prevalence of about one in 3000 newborns, congenital hypothyroidism (CH) is the leading cause of preventable mental retardation and growth failure. The objective of this work is to clarify the contribution of thyroid scintigraphy (TS) using technetium 99 m for the diagnosis of CH and this through the experience of the nuclear medicine department in Sahloul university Hospital.
Materials and methods
This is a retrospective study including 31 children diagnosed with CH, who were referred to the nuclear medicine department of Sahloul Hospital for a thyroid scintigraphy. The average age was 24 months (ranging from 1 month to 14 years). All patients benefited from an acquisition of images centered on the cervical region using the Pinhole collimator in anterior incidence, supplemented by a static acquisition centered on the abdomen 20 minutes after an intravenous injection of 37 to 185 MBq of technetium 99 m.
Results
The study included 18 girls and 13 boys with a sex ratio equal to 1.38. Four patients had Down's syndrome and two patients had a congenital heart defect. Twelve patients (38.7%) had thyroid dysgenesis (6 agenesis and 6 ectopia). Nineteen patients (61.3%) had a thyroid in place with a different level of thyroid fixation (normal fixation (22.6%), high fixation (16.1%) and homogeneous and weak fixation (22.6%) suggesting a disorder of hormonogenesis.
Conclusion
Technetium-99 m thyroid scintigraphy helps in the identification of thyroid dysgenesis, which is the most common cause of CH. The use of iodine 123 with a perchlorate test is particularly preferred in the diagnosis of a hormonogenesis disorder. However, in the absence of iodine 123, as for the case in our country, technetium 99 m ST can be an acceptable alternative allowing an etiological orientation of CH.

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AEP988

Clinical scoring systems fare poorly among elderly patients in diagnosing primary hypothyroidism

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Background
Clinical scoring systems were used traditionally in the diagnosis of hypothyroidism before biochemical diagnosis became the norm. There are two well validated clinical scoring systems (Billewicz and Zulewski) for diagnosing hypothyroidism. Both these scores were validated in younger patients with hypothyroidism and may not be useful in older patients. We conducted this study to determine the clinical utility of these two scoring systems among patients over the age of 60 years for diagnosing hypothyroidism.
Aims and objectives
To determine the sensitivity and specificity of the Billewicz diagnostic index and Zulewski clinical score in diagnosing hypothyroidism in elderly subjects suspected to have hypothyroidism.
Materials and methods
This observational study was conducted in the Departments of Medicine and Endocrinology at tertiary care university affiliated teaching hospital from December 2017 to September 2019. After informed consent, clinical data and scoring of the patients was collected in elderly subjects ($n=200$) with suspected hypothyroidism. A biochemical diagnosis of primary hypothyroidism was considered the gold standard (raised TSH levels with a low FT4 levels).
Results
Billewicz score was 99.32% specific and 1.85% sensitive, while specificity and sensitivity of Zulewski score was 80.82% and 37.04% respectively (considering indeterminate scores as euthyroid). After considering Indeterminate as hypothyroid, sensitivity of Billewicz and Zulewski score was 75.93% and 70.37%; and specificity was 20.55% and 36.99% respectively. Only the Zulewski score (indeterminate as euthyroid) showed weak significant agreement with final diagnosis of hypothyroidism ($K=0.185$, $P=0.009$).
Conclusion
Both scoring systems do not help in the diagnosis of hypothyroidism among elderly patients.
Keywords: thyroid gland, hypothyroidism, billewicz diagnostic index, zulewski clinical score, indeterminate.
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AEP989

Effect of cholecalciferol treatment on insulin sensitivity in patients with chronic autoimmune thyroiditis

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Background
Effects of vitamin D on immune cells might affect diabetes mellitus (DM) development since inflammatory factors have been linked to insulin resistance (IR). The aim of this study was to investigate the effect of cholesterol treatment on insulin sensitivity metabolic markers in patients with chronic autoimmune thyroiditis.
Materials and methods
In this double-blind, randomized, placebo-controlled trial, which was conducted from May to September 2019, 45 patients with chronic autoimmune thyroiditis were enrolled. They randomly allocated into two groups to receive oral cholecalciferol (28 000 IU weekly) and placebo for 12 weeks. Serum concentration of glycated hemoglobin (HbA1c), insulin, fasting plasma glucose (FPG), calcium, phosphorus, parathyroid hormone, C-reactive protein, creatinine, triglyceride (TG), total cholesterol, and high-density lipoprotein were measured in both groups before and after investigation. Homeostasis model assessment estimates of beta cell function (HOMA-B) and HOMA-insulin resistance (HOMA-IR) were calculated before and after trial in both groups.
Results
Twenty-three and twenty-two participants were allocated to cholecalciferol-treated and placebo-treated groups, respectively. Mean (standard error) level of 25(OH)D increased significantly in cholecalciferol-treated group (34.71 [1.82] ng/ml vs 14.17 [0.72] ng/ml, $P=0.002$). Plasma parathyroid hormone decreased in the treatment group while remaining unchanged in the placebo-treated group (35.04 [2.24] ng/ml vs 46.83 [2.29] ng/ml respectively, $P=0.03$). In between-group comparison, there was significant difference between cholecalciferol-treated and placebo-treated groups regarding measures of HOMA-B, HOMA-IR ($P<0.05$). Other variables did not meet a significant change after trial ($P=$NS).
Conclusions
Weekly 28 000 IU oral cholecalciferol for 12 weeks improved IR and insulin secretion in patients with chronic autoimmune thyroiditis.
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AEP990

The introduction of endoscopic techniques in thyroid surgery

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Introduction
Endoscopic surgery has found wide application in many areas of medicine in a short: endocrinology is no exception. The main advantages of endoscopic access to the thyroid gland are the possibility of conducting endovideoscopy, a low traumatic surgical intervention, shortening of the inpatient treatment duration, periods of incapacity for work, and cosmetic effects
Goal
Determine the appropriateness of using endoscopic technologies in comparison with classical techniques in thyroid surgery procedure.
Material and methods
During last decade, more than thousand patients with diffuse and nodular thyroid disease got thyroid surgery in the surgical department of the Brest Regional Hospital (Belarus). All patients with nodular pathology of thyroid gland underwent fine needle aspiration biopsy under ultrasound control and got cytology conclusion of nonmalignant disorder. Thyroid status was investigated in all cases (TSH, free T3 and T4, TPO-Ab). TSH receptor antibodies (TSHR-Ab/TBII) were analyzed in patients with the suppression of TSH levels, thyroid scintiography was also performed in such cases. As a routine – during surgery, all patients underwent an express biopsy. All the cases of thyroid surgery were divided depending on the type (traditional or endoscopic surgery) and volume of surgical intervention (hemi or total thyroidectomy).
Results
The results of surgical treatment of patients with thyroid diseases in a traditional way and endoscopically were evaluated according to the following parameters: the duration of surgery, intraoperative volume of blood loss, drainage of the postoperative wound, the intensity of the pain in the postoperative period, complications, the duration of hospitalization in the postoperative period, cosmetic effect. In the group of endoscopic thyroid surgery, the average length of the hospital staying was reduced to a day. Intraoperative complications occurred in 1 (0.9%) patient. Postoperative complications developed in 7 (6.2%) patients. Transient paresis of the recurrent laryngeal nerve (RN) in 5 (4.4%) patients could not be avoided. The patients who underwent surgery endoscopically, the intensity of the pain in the postoperative period was much lower compared to the usual technique. Also, a decrease in the number of intra- and postoperative complications during the endoscopic thyroid surgery was reliably established.
Conclusions
The introduction of endoscopic interventions impoves the possibility of obtaining optimal clinical results in patients with thyroid nodular diseases and reduces the number of postoperative complications, shorten the length of the patient's stay in the hospital and the interval of rehabilitation in the postoperative period with good cosmetic effect in the operation area.
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AEP991

Efficacy of radioactive iodine in treatment of graves' disease

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Background
Radioactive iodine ^{131}I (RAI) treatment is an effective definitive treatment of hyperthyroidism, used as a first line or second line treatment.
Aims and objectives

1. To evaluate the response of RAI therapy in Graves' disease.
2. To determine any factors predicting treatment failure.

Study design
Retrospective study
Materials and methods
Clinical records were reviewed and data were collected about hyperthyroid patients. Thyrotoxicosis was diagnosed on the basis of elevated total T4 (50–110 ng/ml) and/or total T3 (0.87–1.78 ng/ml) values with suppressed TSH. The etiology of hyperthyroidism was established with 99 mTc-pertechnetate thyroidimaging and the gland size was measured with ultrasound. Empirical single dose, approximately 10 mci of I-131 was used for ablation. Ablation was done after stoppinganti thyroid medications for at least 3 days prior to RAI therapy, and drugs were restartedafter 2 days.
Post ablation, biochemical monitoring was done once a month. Successful RAI therapy for hyperthyroidism was defined as clinical and biochemical euthyroid or hypothyroid status (group 1). Treatment failure was defined as persistent of hyperthyroidism even after 6–12 months post-RAI therapy (group 2).
Patientswho underwent RAI ablation for Graves disease and whose complete follow up records available were included in the study. Patients who had toxic adenoma and toxic MNG were excluded from the study.
Results
Total 70 patients were recruited,19 patients were excluded due to incomplete data. Fifty one patients were included. Age at diagnosis of hyperthyroidism was 38 ± 9.7 years. Men to women ratio was 1:6.3. Postablation (mean dose of I-131 9.6 ± 0.8 mci), 32 patients (62.7%) achieved remission (group 1). Among these 30 patients became hypothyroid and 2 patients became euthyroid. Nineteen patients (37.3%) failed to achieve remission(group 2). Time for response ingroup 1 was 4.9 ± 2.2 months. Thyroid gland was larger in size in the group 2 (19.9 ± 6.0 gm) as compared to group 1 (10.4 ± 3.8 gm). Mean age at diagnosis was similar among both the groups (group 1:37.3 ± 7 years vs group 2 : 39 ± 13.3 years). There was no difference in the male to female ratio and pre ablation T3, T4 levels, between the two groups.
Conclusion
Sixty three percent of the patients achieved complete remission with a single dose of I-131 with in 5 months. Larger gland size predicted the treatment failure. No other demographic, and biochemical parameters were different between two groups.

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AEP992

Thyroid cancer recurrence risk after transplantation: Single center experience

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Introduction
There is little data about the influence of immunosuppression on the recurrence rate of thyroid cancer. We aimed to evaluate the risk of recurrence and mortality of thyroid cancer after solid organ transplantation.
Patients and methods
We retrospectively evaluated 802 kidney and 283 liver transplant recipients who underwent transplantation between January 1999 and May 2019 in Başkent University. We identified 14 patients with thyroid cancer. Of these 14 patients, 12 were kidney transplant recipients and 2 were liver transplant recipients. Thyroid cancer was classified as low/intermediate and high risk according to the 8th pTNM (tumor, node, metastasis) classification system as well as American Thyroid Association guidelines.
Results
Fourteen patients (seven males, seven females) with a history of both organ transplantation and thyroid cancer were recruited for this study. Median age of the patients was 42 (31–70) years. All of the patients were on corticosteroid,and mycophenolate mofetil was administered to 13 patients (92.9%), cyclosporin A to 10 patients (71.8%), tacrolimus to 1 patient (7.1%), and-Mammalian target of rapamycin (mTOR) inhibitors were used in 2 patients (14.3%). All patients underwent total thyrodectomy, except one patient who underwent total thyroidectomy and lateral neck dissection. Median age at diagnosis of thyroid cancer was 34 (18–65) years. Six of the patients (42.9%) were diagnosed pre-transplantation. Thirteen of the patients had papillary and one patient had follicular cancer. Nine of the patients (64.3%) had multifocal disease. All patients had stage I disease and also were in low risk group. Median follow-up time was 6.9 (1.3–14.6) years. After initial treatment, 13 of 14 patients were in remission. One patient with had local recurrence During the follow-up period, there were no signs of local recurrence or distant metastasis in the remaining 13 patients. None of the patients were lost to thyroid cancer.
Discussion
Our results suggest that solid organ transplantation does not influence thyroid cancer prognosis, especially in low risk patients. There is a concern about the progression of a previously treated cancer after transplantation. In this study, six of the patients were diagnosed and treated before transplantation. During follow-up, all of the patients were in remission. This indicates that transplantation may not alter the outcome of differentiated thyroid cancer.
In conclusion, our study suggests that thyroid cancer outcome is not altered after kidney and liver transplantation. Further studies in a larger population are needed.

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AEP993

125I radioactive seed localization (RSL) in surgery of cervical metastasis of thyroid cancer

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Introduction
The aim of this work is the evaluation of usefulness of radioactive seed localization (RSL) for the detection of cervical recurrence of thyroid cancer in order to improve the surgical outcome.
Material and method
Six patients with thyroid cancer with cervical recurrences evidenced by ultrasound, cytology/Tg-FNAB were selected for this procedure. A ^{125}I seed was placed in the metastatic lesion using a needle guided by ultrasound. During surgery, a handheld gamma probe/portable gammacamera were used for lesion localization and excision. After removing the target issue, it was verified that the seed was included in the excised tissue. Surgical intervention duration, lesion location, seed activity, thyroglobulin level, effective radiation dose, complications and the degree of surgical resection were analyzed.
Results
All the marked nodes were positive in histology. The mean duration of the ultrasound procedure was 12.8 ± 5.2 min. Seed was kept inside the patient, in average, during 4.3 days (3–7) and the average surgical time was 45 ± 37.5 min. We found 13 metastatic specimens. The mean activity of the implanted seed was 70.32 ± 22.7 MBq (42.8–105). The thyroglobulin level was 2.08 ± 1.56 ng/dl. Only one case of transient hypoparathyroidism was found.
Conclusions
The introduction of RSL in our unit has shown benefits for the patient and medical team, being a safe and effective procedure that also improves surgical programming.

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AEP994

Cystic cervical lymphadenopathy revealing thyroid papillary carcinoma

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Introduction
Cervical lymphadenopathy is a frequent reason for ENT consultation. In most cases the diagnosis is easy based on clinical, radiological and cytopathological data. However, in some situations, the diagnosis remains pending. The objective of this work is to study the possible difficulties face to a chronic cystic cervical lymphadenopathy.
Materials and methods

It is a retrospective study bringing 4 cases of cervical cystic lymphadenopathy revealing thyroid papillary carcinoma collected over a period of 17 years (from 2000 to 2016).
Results
Our study focused on 4 cases. The sex ratio was 1 with an average age of 49 years. The reason for consultation was cervical swelling in all cases evolving for an average of 6 years. The swelling was supraclavicular in 2 cases, jugulo-carotid in one case and subdigastric in one case. Its size varied between 3 and 15 cm. The swelling was relapsing in all cases, associated with a palpable thyroid nodule in one case and multiple lymphadenopathies in one case. Cervical ultrasound, done in all patients, wrongly led to the diagnosis of a branchial cyst in 2 cases. All patients had a cervicotomy with an extemporaneous examination, suggesting a metastasis of a thyroid papillary carcinoma in 2 cases. Which examination carried the diagnosis of branchial cyst in the 2 other patients. The metastatic nature of lymphadenopathy was not confirmed until the final histological examination. It was a metastasis of papillary micro carcinoma in 3 cases and of a branchial cyst invaded by an adjacent metastatic lymphadenopathy of a thyroid papillary carcinoma in one case. The cystic nature was confirmed after immunohistochemical study.
Conclusion
Cystic cervical lymphadenopathy may be the only telltale sign of papillary carcinoma of the thyroid, hence the need to invoke this diagnosis before any cystic cervical mass.

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AEP995

Performance of a dual-component molecular assay in cytologically indeterminate thyroid nodules

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Background
Deciding whether patients with a cytologically indeterminate thyroid nodule should be referred for surgery or for active surveillance is an important challenge for clinicians. The aim of this study was to evaluate the performance of a novel dual-component molecular assay as an ancillary molecular method for resolving indeterminate thyroid nodule cytology.
Methods
We selected 156 thyroid nodules from those that had undergone both FNA cytology and surgical resection between June 2016 and December 2017. The sample set included 63 nodules cytologically classified as *indeterminate*, and 93 other nodules randomly selected from those with *non-diagnostic*, *benign*, *suspicious or malignant* cytology. Nucleic acids from each nodule were subjected to next-generation sequencing analysis for mutation detection in 24 genes and to digital-PCR evaluation for miR-146b-5p expression levels.
Results
Used alone, mutation analysis in the indeterminate subset (cancer prevalence:22.5%) displayed high sensitivity (89%) and NPV (96%). In contrast, the miR-146b-5p assay offered high specificity (93%) and PPV (93%). Combined use of both analyses eliminated all the false-negative results (100% sensitivity, 100% NPV).
Conclusions
These preliminary data suggest that a dual-component molecular test can increase the diagnostic accuracy of thyroid cytology alone by reducing the number of nodules that will be classified as indeterminate and increasing those that can be reliably classified as benign. If these findings are confirmed, this test can be considered for use in clinical practice and is expected to reduce diagnostic surgery and health care costs, and to improve patient quality of life.

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AEP996

Comparison of therapeutic radioiodine dose to ablation response in differentiated thyroid cancer patients with cut-off serum thyroglobulin level after two weeks of levothyroxine withdrawal

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Purpose
This retrospective study is evaluated the efficacy of three doses of I-131 (1110 MBq vs 3700 MBq vs 5550 MBq) in differentiated thyroid carcinoma patients with cut-off serum thyroglobulin (TG) level after two weeks of thyroid hormone withdrawal for postoperative thyroid remnant ablation.
Methods
A total of 97 patients with differentiated thyroid cancer treated with total thyroidectomy and radioactive iodine (RAI) therapy were enrolled. Doses of 1110 MBq, 3700 MBq, and 5550 MBq were determined based on the surgical records and pathologic results of each patient. Serum TG test was performed one week before radioiodine treatment and two weeks after the thyroid hormone stoppage(preTG; ng/dl) and cut-off preTG level was below 5 ng/dl. After six months of RAI treatment, complete ablation,which defined as showing no uptake in diagnostic I-131 scan, stimulated TG of less than 1.0 ng/dl, and TG antibody of less than 100 ng/dl was investigated, and statistically analyzed.
Results
After initial therapy, 76 patients (78.4%) were in complete ablation, with 77.8% (7/9) in 1110 MBq group, 80.0% (60/75) in 3700 MBq group, and 69.2% (9/13) in 5500 MBq group. There was no statistically significant difference in complete ablation between different radiation dose groups ($P=0.681$). Serum preTG level did not show a statistically significant difference between the three groups ($P=0.091$). The serum preTG level (adjusted odds ratio (OR)=1.70, 95% confidence intervals (CI) 1.07–2.69, $P=0.024$) and stimulated TG level at the time of RAI (adjusted OR=1.4, 95% CI 1.14–1.68, $P<0.001$) were significantly independent predictors of complete ablation.
Conclusion
RAI therapy with 1110 MBq seems to besufficient for ablation if thepreTG level was below 5 ng/dl in patients with differentiated thyroid cancer.

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AEP997

Case report: Myocardial Infarction after 9 month treatmentwith a tyrosine kinase inhibitor (TKI) with Anti-VEGF receptor activity

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Introduction
TKIs including anti-VEGF receptor activity have been approved for the treatment of patients with radioiodine resistant thyroid carcinomas. For lenvatinib arterial thromboembolic events are listed as adverse events of special interest. In the phase III study of SELECT trial, arterial thromboembolic events were reported in 3% of lenvatinib-treated patients and 1% in the placebo group. Most of the patients had predisposing factors. Only one myocardial infarct was reported in the lenvatinib phase III study.
Patient
We report a 67 year-old-female with metastatic folicular thyroid carcinoma at time of diagnosis (bone, hepatic, lung and renal metastasis). Total thyroidectomy was performed. Zolendronate was started and radiotherapy was administired due to spinal cord compression caused by metastasis on L3, L4, L5. NO radioidine therapy was administired as it was considered radioiodine resistant (No RAI uptake) and treatment with Sorafenib was started. Sorafenib treatment resulted in disease progression with appearence of new hepatic and lung metastasisso treatment with sorafenib was discontinued and Lenvatinib was started with partial response. During further treatment with lenvatinib with dose reduction from initially 24 to 10 mg at 6 months of lenvatinib treatment a myocardial infarction occurred after 9 months of lenvatinib treatment. Coronary angiographydid not show significant coronary stenosis or structure abnormalities and echocardiography showed normal results with preserved ejection fraction. Treatment with lenvatinib was discontinued at the time of diagnosis of the myocardial infarction. Except for well controlled hypertension there were neither predisposing diseases like diabetes nor symptoms of cardiac ischemia on exertion

Conclusion
Our case report suggests that lenvatinib should also be added to the list of TKIs with ATE potential. So far, most of the thromboembolic events appeared after short-term treatment median duration of 10.8 months with tyrosine kinase inhibitors and mostly in patients with predisposing factors. However, our patient suffered from her first myocardial infarction aftertreatment with lenvatinib for 9 months, in absence of predisposing diseases except well controlled hypertension. Therefore, as previously proposed by Conti *et al.* for other TKIs also patients with lenvatinib treatment should be assessed for cardiovascular risk and coronary ischemia before and during the treatment

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AEP998

Mental health in children and adolescents with graves disease

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Aim
To study the thyroid and cognitive status and psycho-emotional health of children and adolescents with Graves' disease (GD).
Materials and methods
37 children and adolescents with GD examined in the Republican Medical Center of Endocrinology (Uzbekistan). The control group consisted of 19 healthy children and adolescents. Thyroid status was determined using a closed-type immunochemistry analyzer Cobas e411 Hitachi from Hoffman-LeRoche (Switzerland) and its reagents. To assess the level of intelligence of children, standard progressive Raven matrices were used. Spielberg Questionnaire (State-Trait Personal Inventory) was used to determine anxiety syndrome. The differences were considered statistically significant at $P<0.05$.
Results
In Uzbekistan, according to the annual statistical report for 2018, the dispensary includes 145 children and adolescents with GD. We examined 37 children with GD, which amounted to 25.5% of all children with GD in Uzbekistan. At the time of the first treatment, all children with GD had a pronounced thyrotoxicosis clinic with a reliably low TSH level (0.014±0.024, $P<0.01$), high fT4 values (5.1±0.2, $P<0.05$) and TRAbs interval was 2.5–40.0 IU/l with a median (Me) of 11.6 (17.0±1.1, $P<0.0001$). In the same group, 83.8% (31) showed high values of TPO Ab. In the control group, 8.3% (1) also showed elevated levels of TPO Ab. In a group of GD, 100% of children showed a high level of anxiety, 70.3% (26) showed a high degree of negative emotional experiences and low cognitive activity. Children with GD were dominated by indicators of insecurity, anxiety, self-distrust, a sense of inferiority and hostility, a tendency to conflict, difficulties in communication, and depression were noted. The total IQ adjusted for age in children and adolescents with GD was 73.9±14.8 (min 55, max 96, Me 75). In the control group, this indicator was 120.2±7.5 points (min 106, max 133, Me 115; $P<0.001$). In the group with GD, no children with extraordinary intelligence were detected. In 43.2% (16) adolescents, the IQ level corresponded to an average degree of intelligence, in 56.8% (21) it was below average. At the same time, 51.4% (19) of children in this group showed endocrine encephalopathy.
Conclusions
In all adolescents with thyrotoxicosis, anxiety, and negative emotional experiences prevailed, while the cognitive activity in these children was lower in comparison with the control group. Children with GD have defects in intellectual ability and impaired attention and/or perception.

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AEP999

Pembrolizumab inducing thyroid diseases: Are there differences between patients treated for lung carcinomas and those for lymphomas?

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Background
In the last years, Pembrolizumab has been used to treat solid and lymphatic neoplasms, showing improved patients' survival. Due to its mechanism of action, Pembrolizumab may be responsible of several immune-related adverse events (irAEs). The most frequent endocrine-irAEs reported are thyroid diseases.
Aims
The aim of this study was to evaluate differences in thyroid disease incidence and presentation between patients treated for lung cancer and those for lymphomas.
Materials and methods
Data of patients treated with flat dose of Pembrolizumab (200 mg/3 weeks) for lymphoma and for lung cancer, attending the Institute of Hematology Seràgnoli and the Oncology Unit of Bologna respectively, were retrospectively collected. Blood tests for thyroid function were drawn at baseline and before each injections.
Results
We included 69 patients, 37 with lung cancer (26 adenocarcinoma; 11 squamous cell carcinoma) and 32 with lymphoma (19 nodular sclerosis Hodgkin lymphoma; 13 primary mediastinal B-cell lymphoma).Pembrolizumab was administered in both cancer population for a similar amount of time (lung cancer: median of 21 weeks, lymphoma median of 25; $P=0.330$). The follow up was different according to the evolution of cancer type(lung cancer median of 21 weeks, range: 6–111; lymphomas for 115 weeks, range: 4–208; $P<0.001$). Patients with lung cancer were older than those with lymphoma (median: 33 years, range: 18–68 vs median: 70, range: 50–82; $P<0.001$). Thyroid disease prevalence was similar (10.8% for lung cancer and 9.4% for lymphoma, $P=0.844$). In particular, 3 patients developed thyrotoxicosis and 1 hypothyroidism in the lung cancer population, while 1 thyrotoxicosis and 2 hypothyroidisms were found in the lymphoma ones. In all patients, thyrotoxicosis was an early event, occurring between the 2nd and 5th administration of Pembrolizumab, while hypothyroidism arose later, between the 7th and 14th cycle. The clinical presentation and progress of thyroid diseases were equal between the two cancer populations. Thyrotoxicosis was asymptomatic and reversible, whereas the hypothyroidism was clinically mild (grade 2) but permanent, requiring long-life replacement therapy. In all subjects Pembrolizumab was continued despite thyropaties onset. No differences in TSH values before Pembrolizumab adminstration were found between patients who developed thyropathies and the remaining patients ($P=1.000$ for lung cancer and $P=0.637$ for lymphoma).
Conclusion
No differences for frequency, characteristics and evolution of thyroid diseases were shown in patients treated with Pembrolizumab in solid and hematologic malignancies. The type of tumours and age at treatment are not associated with the development of drug-induced endocrine adverse events.

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AEP1000

Long-noncoding RAN negatively regulated by thyroid hormone to suppress tumorigenesis

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Long non-coding RNAs (lncRNAs) are a class of non-protein coding transcripts longer than 200 nucleotides that regulate complex cellular functions, such as cell growth, differentiation, metabolism, and metastasis. Thyroid hormone (T3) and its receptor (TR) are involved in cancer progression. To identify T3/TR-related lncRNAs that are differentially expressed in HCC, lncRNA expression profile screening was performed using the SYBR Green-based quantitative reverse transcription-PCR (qRT-PCR) array in TR-overexpressing HepG2 cell lines and hepatocellular carcinoma (HCC) specimens. The deregulation of lncRNA expression has been detected in many tumor types, the mechanisms underlying specific involvement of lncRNAs in tumorigenicity remain unclear. Candidate lncRNAs that were simultaneously downregulated by T3/TR and upregulated in HCC were selected for further study, leading to the identification of lncRNA-LOC34 578. LOC34 578 was significantly upregulated in HCC compared to normal tissues. Furthermore, expression of LOC34 578 was significantly positively correlated with overall and recurrence-free survival of HCC patients. Notably, LOC34 578 expression was positively correlated with tumor type, vascular invasion, and pathological stage. These findings suggest that LOC34 578 plays an important regulator in hepatoma. Furthermore, we examined the potential effects of LOC LOC34 578 on hepatoma cell migration and invasion. HCC cells with knockdown of LOC34 578 were further

established. Overexpression of LOC34 578 enhanced cell migration ability. On the other hand, knockdown of LOC34 578 significantly suppressed cell migration and invasion, compared with that in cells transfected with control. To further confirm LOC34 578 regulated cell motility, cell migration was measured in LOC34 578-overexpressing cells simultaneously knockdown of LOC34 578. The results indicated LOC34 578 was involved in regulating hepatoma cell motility. To confirm whether the *in vitro* phenotype of LOC34 578 is reproducible *in vivo*, the effect of LOC34 578 knockdown on HCC cell tumor formation was examined in nude mice. The knockdown of LOC34 578 reduces tumor growth compared to the control group. Accordingly, LOC34 578 acts as oncogenic lncRNA in HCC. To assess whether LOC34 578 contributes to the activities of EMT, EMT-related genes were examined. The levels of p-STAT3 and MMP2 were lower in LOC34 578-depleted HCC cells relative to their control. E-cadherin, p21, and p27 were higher in knockdown of LOC34 578 cell lines. These findings suggest that LOC34 578 modulated cell migration and cell growth through regulations of EMT-related genes, cell cycle-related markers.

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Hot Topics (Including COVID-19)

AEP1001

Obstructive sleep apnea in primary aldosteronism is associated with cortisol cosecretion

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Background
Primary aldosteronism (PA) is a secondary form of arterial hypertension that – in case of unilateral disease – can be cured by surgery. Multiple studies have shown that PA patients are at higher risk to suffer from cardiovascular events and to develop metabolic diseases. Two thirds of patients with PA suffer from obstructive sleep apnea (OSA). A bi-directional, pathophysiological interplay between OSA and PA has been proposed, with focus on overnight rostral fluid shift and the metabolic syndrome. Cortisol cosecretion – a newly identified trait of PA patients – is associated with metabolic risk parameters, independently of mineralocorticoid excess.
Objective
While the connection between the extent of cortisol oversecretion and OSA in overt Cushing's disease has been established, the role of cortisol cosecretion has not been investigated in the relationship of PA and OSA.
Methods and results
We report the results of 31 PA patients who were screened for OSA and hypercortisolism (1-mg overnight dexamethasone suppression test, 24-hour urinary free cortisol determination and late-night salivary cortisol measurement) before initiation of treatment. Serum cortisol values after dexamethasone suppression tests were significantly higher in OSA patients (1.6 µg/dl [1.3; 2.5] vs 1 [1; 1.2], $P=0.002$) and increased with OSA severity (moderate and severe OSA, 2.0 µg/dl [1.5; 2.5] in comparison to mild OSA, 1.4 µg/dl [1.2; 1.9] or no OSA, 1 µg/dl [1; 1.2], $P=0.016$). When adjusting these results for BMI, age, systolic blood pressure and HbA1c values the results remained significant ($P=0.042$).
Conclusions
The main finding of our study is the association of OSA with biochemical evidence of cortisol cosecretion in patients with PA. In this concept, PA induces fluid retention and rostral fluid shift leading to OSA in vulnerable subjects (male, obese patients), inducing increased night-time hypoxia and stress including hypothalamic pituitary adrenal axis activation. This observation can explain the strong links found between cortisol cosecretion, obesity, the metabolic syndrome and primary aldosteronism. Further interventional studies are warranted to determine long-term outcome of CPAP treatment on cortisol cosecretion for this patient cohort.

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AEP1002

Intact endothelial epoxyeicosatrienoic acids pathway in primary aldosteronism – the route to new treatment strategies?

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Rationale
Endothelial dysfunction (ED) is a hallmark of primary aldosteronism and paves the way for subsequent atherosclerotic disease. Past research has confirmed that one factor involved in ED is disturbed nitric oxide (NO) signalling. Since defects in NO release alone cannot explain the whole effect, we set out to address the role of endothelial CYP-expoygenase products (epoxyeicosatrienoic acids, EETs) in aldosterone-mediated endothelial dysfunction.
Objective
Todelineate aldosterone-mediated changes in expression patterns of critical genes which are necessary for the generation of EETs in endothelial cells and their action in smooth muscle cells;to assess stimulated EET release from endothelial cells after chronic aldosterone excess; and tomeasure smooth muscle calcium response to EETs after chronic aldosterone excess. To account for potential co-stimulation of mineralocorticoid receptors, are exposed to physiological levels of cortisol and pathologically relevant levels of aldosterone in parallel.
Methods and results
We show with qPCR and western blot that aldosterone excess in primary human coronary artery endothelial and smooth muscle cells does not change the expression of relevant enzymes (CYPepoxygenases, epoxide hydrolases) and channels which are deemed to be vital for an effective EET pathway. We further demonstrate BKCa channels to be mostly downregulated by physiological levels of glucocorticoids in a glucocorticoid receptor-dependent manner. Aldosterone at concentrations found in patients with primary aldosteronism (1 nM) had only minor impact on BKCa expression. Moreover, we found that stimulated endothelial EET release was unaffected by aldosterone excess. Aldosterone likewise did not induce changes in smooth muscle cell calcium transients to 14,15 EET.
Conclusions
This first systematic investigation of the EET pathway in the context of aldosterone excess demonstrates that neither the endothelial release of nor the smooth muscle response to EETs is seemingly affected by aldosterone excess. Clinical trials aiming to increase the concentration of EETs by inhibiting their breakdown are thus very likely to be effective. We also disentangle the relationship between mineralo- and glucocorticoids on BKCa channel expression. These findings have potential implications for conditions of endogenous or iatrogenic glucocorticoid excess as well as glucocorticoid co-secretion in primary aldosteronism.

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AEP1003

The NOS3 and CYBA gene polymorphisms are associated with subclinical atherosclerosis and arterial stiffness in premenopausal women

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Introduction
Differences in the prevalence and prognosis of cardiovascular disease have been linked with gender specific risk factors as well as the differential impact of sex hormones. Moreover, specific genetic polymorphisms may increase further the risk of cardiovascular disease development. Polymorphisms of genes encoding the NADPH/NADPH oxidase system and the endothelial nitric oxide synthase (eNOS) have been associated with atherosclerosis in the general population, but their significance in reproductively active women remains underexplored. We aimed to investigate the potential association between the C242T polymorphism of the CYBA gene and the G894T polymorphism of the NOS3 gene with the development of subclinical atherosclerosis in young women.
Methods
This cross-sectional study recruited a total of 70 healthy, normally ovulating, reproductively active women. Fasting venous blood samples were obtained for genotyping, using real-time PCR, as well as for hormonal and biochemical assessment. Sonographically assessed indices of vascular structure and function included carotid and femoral intima-media thickness (IMT), flow-mediated dilation (FMD) and carotid-femoral pulse-wave velocity (PWV).
Results
The prevalence of genotypes was as follows: for the C242T polymorphism, wild type in 38.6% (27/70), heterozygote in 31.4% (22/70), and homozygote in 30.0% (21/70); for the G894T polymorphism, wild type in 44.3% (31/70), heterozygote in 54.3% (38/70), and homozygote in 1.4% (1/70). Presence of the heterozygous genotype of the C242T polymorphism associated significantly with internal carotid IMT (b-coefficient=−0.119, $P=0.011$) and combined-IMT (b-coefficient=−0.061, $P=0.015$), after adjustment for traditional risk factors in the multivariable analysis. Values of FMD were associated with systolic blood pressure, lipids and the presence of the heterozygous C242T polymorphism (FMD, b-coefficient −1.604, $P=0.034$). In the univariate analysis, carriers of the G894T NOS3 polymorphic variant had had higher values of IMT and PWV compared to the wild-type subgroup (carotid bulb-IMT and PWV, heterozygotes/homozygotes vs wild type 0.7±0.2 vs 0.6±0.1 mm; 7.1±0.8 vs 6.6±0.7 m/s; $P=0.048$ and $P=0.029$, respectively). These differences, however, were rendered non-significant in the multivariable analysis.
Conclusion
The CYBA C242T polymorphism is associated with subclinical atherosclerosis of the carotid arteries as well as with endothelial function, in healthy reproductively active women. The NOS3 G894T polymorphic variant also associated with indices of subclinical atherosclerosis, however this association is possibly mediated by the effect of traditional cardiovascular risk factors. The significance of these findings in the clinical setting remains to be elucidated by larger prospective studies.

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AEP1004

Impact of covid-19 pandemic on psychophysical stress in patients with adrenal insufficiency: The corti-covid study

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Background
COVID-19 pandemic is a novel, potentially adverse condition for patients with adrenal insufficiency (AI), whose life expectancy and quality of life (QoL) are impaired due to their risk of infections and stress-triggered acute events. Therapeutic usefulness of glucocorticoids in COVID-19 is debated, but infected AI patients require prompt replacement tailoring.
Objectives
In a cohort of AI patients, to assess:
– the prevalence, manifestations and outcome of COVID-19;
– the prevalence of adrenal crises and their possible association with intercurrent COVID-19 and/or pandemic-related psychophysical stress;
– the emotional impact of the pandemic-induced social distancing;
– the self-reported QoL and health status during the lockdown.
Study design
Open-label, cross-sectional, monocentric study (University Hospital of Ancona, Italy) covering the period February-April 2020.
Patients and methods
121 patients (59 males, 55±17 years) with primary ($n=40$) and secondary ($n=81$) AI underwent a three-questionnaire telematics interview:
– purpose-built 'CORTI-COVID' questionnaire (34 items, 4 domains), assessing the latest medical history and the degree of concern (score 1–5) for COVID-19-related global health, AI-specific personal health, occupational consequences, economic impact and social implications;
– AddiQoL-30;
– Short-Form-36 Health Survey (SF-36).
Results were analyzed according to AI etiology. Demography, glucocorticoid replacement and comorbidities impacting COVID-19 prognosis were also considered.
Results
COVID-19 occurred in one (0.8% prevalence) 48-year-old woman with primary AI, who promptly adjusted glucocorticoid replacement. Dyspnea lasted 3 days, without requiring hospitalization. COVID-19 was not reported among alive secondary AI patients. No adrenal crises were experienced, but pandemic-related psychophysical stress accounted for 6/14 glucocorticoid stress doses. Mean CORTI-COVID score was similar between primary and secondary AI patients. The most influencing items were 'personal health' for the former ($P=0.881$, $P=0.000$) and 'economy' for the latter ($P=0.809$, $P=0.000$). Occupational concern was higher for patients affected by working restrictions. Demography, glucocorticoid replacement and comorbidities played no significant role. Mean AddiQoL-30 score was 131±27 and 131±25 for primary and secondary AI, respectively. Global and single-item CORTI-COVID scores were all inversely correlated with QoL. SF-36 correlated directly with AddiQoL-30, inversely with CORTI-COVID. Physical pain and general health perception were influenced by glucocorticoid dose in secondary AI. Comorbidities and, for secondary AI, gender significantly impacted both AddiQoL-30 and SF-36 scores.
Conclusions
If educational efforts are made to prevent acute events, both primary and secondary AI patients seem not at particular risk of COVID-19. CORTI-COVID is a novel, reliable questionnaire assessing the strong pandemic-related emotional burden for AI patients. Even in unconventionally stressful situations, educated patients with AI preserve a good QoL.

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AEP1005

Adrenal insufficiency at the time of COVID-19: A retrospective study

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Background
COVID-19 represents a global health emergency and infected patients with chronic diseases often present a severe impairment. Adrenal insufficiency (AI) is supposed to be associated with an increased risk of infections which could trigger adrenal crisis. Our primary aim was to evaluate the incidence of COVID-19 symptoms and complications in AI patients.
Materials and methods
We conducted a retrospective case-control study, in 279 patients with primary and secondary AI and 112 controls. By administering a standardized questionnaire by phone, we collected data on COVID-19 suggestive symptoms and consequences. As symptoms we included fever, cough, myalgia, fatigue, dyspnea, gastrointestinal symptoms, conjunctivitis, anosmia, ageusia, upper respiratory tracts symptoms, thoracic pain, headaches and otalgia. Controls were represented by patients with benign pituitary non-functioning lesions, without hormonal alterations. All patients were on active follow-up and lived in Lombardy, one of the most affected territory. All AI patients had been previously trained to modify their replacement therapy on stress doses.
Results
AI and controls' characteristics (age, sex distribution, smoking and working habit) were comparable. In February-April 2020, the prevalence of symptomatic patients (complaining at least one symptom of viral infection) was similar between the two groups (24% in AI and 22.3% in controls, $P=0.788$). Highly suggestive COVID-19 symptoms (at least two including fever and/or cough) also occurred equally in AI and controls (12.5% in both groups). No patient required hospitalization and no adrenal crisis was reported. In about 30% of symptomatic AI patients, replacement therapy was correctly increased. Few nasopharyngeal swabs were performed ($n=12$) as indicated by sanitary regulations, limiting conclusions on the exact infection rate (positive result in 0.7% of AI patients and 0% of controls, $P=0.515$).

Conclusion
AI patients who are adequately treated and trained, seem to display the same incidence of COVID-19 suggestive symptoms and disease severity as controls.

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AEP1006

Variable mineralocorticoid function in autoimmune Addison's disease – a case report

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Autoimmune Addison's disease (AAD) is widely believed to be associated with total loss of endogenous mineralocorticoid and glucocorticoid production and secretion, due to cell-mediated immune destruction. Therefore, patients with AAD are prescribed lifelong mineralocorticoid and glucocorticoid replacement therapy. We present a case of a 69 year old women known with polyglandular autoimmune disease type 2 (hypothyroidism, Addison's disease and premature ovarian failure) diagnosed 30 years ago, who required full replacement therapy with glucocorticoids, while mineralocorticoid replacement could be withheld. Several times through the disease course, replacement therapy with low dose synthetic mineralocorticoid was initiated, but had to be withdrawn due to development of hypertension, hypokalaemia and marked oedema of the lower limbs. Blood samples showed residual aldosterone secretion, albeit with high renin levels. After interruption of fludrocortisone acetate, she had persistent normal blood pressure, sodium levels and high normal potassium levels. She was recently admitted for a first severe Addison crisis due to SARS-CoV-2 infection. The patient presented with marked hyperkalaemia and low sodium levels, reacting quickly to stress glucocorticoid replacement therapy. Under three times 20 mg of hydrocortisone daily, aldosterone was not measurable and plasma renin increased to 62 ng/l (normal values: 0.1–16.1 ng/l), indicating variable residual mineralocorticoid secretion. This case highlights the possible variability among patients with AAD in residual adrenal function, questioning the dogma of total loss of function currently accepted in endocrinology. Indeed, a recent study shows variable residual mineralocorticoid and glucocorticoids levels in blood of patients with AAD. In some case reports the documentation of residual or recovered glucocorticoid secretion lead to the tapering or withdrawal of hydrocortisone substitution therapy. To the best of our knowledge, this has not been documented for mineralocorticoid substitution therapy. The clinical significance and impact of measurable steroid production by the adrenal glands on treatment remains ill defined. It does not preclude Addison crisis, as illustrated in the present case report. Regular re-assessment of adrenal function should be performed in patient with AAD, in particular in the presence of symptoms of over substation in order to identify cases that can benefit from temporary decrease of glucocorticoid or mineralocorticoid substitution therapy. Even in this setting patient should be educated to adapt or recover treatment in stress situations to avoid Addison crisis.

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AEP1007

Testosterone levels were independently associated to sub-clinical atherosclerosis in men with chronic spinal cord injury

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Background
Men suffering from spinal cord injury (SCI) were at increased risk for cardiovascular diseases (CVD). SCI subjects showed an higher value of carotid intima media thickness (cIMT) at ultrasound, a surrogate markers of sub-clinical atherosclerosis. Furthermore, SCI men exhibited an higher prevalence of androgen deficiency compared to general population.
Objectives
To investigate the relationship between total testosterone (TT) levels and cIMT in men with chronic SCI.
Materials and methods
In this observational and cross-sectional study, cIMT of 60 men with chronic (> 1 years) SCI, aged 56.0 (25th–75th: 46.0–67.2) years, was evaluated with neck ultrasonography. All patients underwent a complete neurological exam, as well as biochemical and hormonal assessment. Comorbidity was scored by Charlson comorbidity index (CCI). Physical activity was assessed by self-administered tool leisure time physical activity (LTPA).
Results
At linear univariate regression analysis cIMT waspositively associated with age (β=0.09, 95% CI : 0.04, –0.15; P=0.008), calculated LDL cholesterol level (β=0.09, 95% CI : 0.03, 0.14; P=0.003) and HOMA-index (β=0.03, 95% CI : 0.001, 0.06; P=0.04). An inverse association were found between cIMT and TT serum levels (β=–0.04, 95% CI : –0.06, –0.15; P=0.001). Multivariate regression analysis, with variables identified at previous analysis, demonstrated that only TT levels were independently associatedto cIMT(β=–0.03, 95% CI : –0.04, –0.009; P=0.009). SCI men with androgen deficiency (TT < 303 ng/dl) showed an higher value of the cIMT (0.15; 25–75th : 0.12–0.24) compared to SCI men with normal androgen status (0.12, 25–75th :0.09, 0.16; P=0.03). In our group, an inverse correlation was found between TT and cIMT (r=–0.52; P=0.003).
Discussion
The relationship between androgen levels and CVD is still debated in the general population. Although, weak evidence suggested that hypogonadal able-walking men were at increased risk to develop CVD, less is known about potential putative association between endogenous testosterone and cardiovascular risk in SCI patients.
Conclusion
Lower TT levels were independently associated to higher burden of cIMT in male suffering from chronic spinal cord injury.

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AEP1008

The association between systolic blood pressure reduction during clonidine suppression testing and the decrease in plasma catecholamines and metanephrines

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Background
Borderline isolatednorepinephrine (NE) and normetanephrine (NMT) elevation is common among patients with suspected pheochromocytoma and paraganglioma (PPGL). The clonidine suppression test (CST) may help establish the etiology in these cases. Prolonged laboratory processing and/or paucity of reliable biochemical assaysmay limit the utility of CST. The aim of this study was to evaluate whether blood pressure (BP) reduction during CST is associated with alterations in plasma NMT/NE, thereby potentially providing an immediate indicationof CST results.
Methods
A cross sectional study, including all consecutive patients with suspected PPGL who underwent CST from 1st January 2014 to 31st December 2019. Linear regression models were conducted to evaluate the association between BP reduction and decrease in plasma NMT/NE.
Results
The final analysis included 36 patients (17 males). The decrease in Systolic BP (SBP) 90 minutes post clonidine was associated with a decrease inplasma NMT (R=0.668, P=0.025) and NE (R=0.562, P=0.005). A 40% decrease in NMT and NE correlated with a 9.74% and 7.16% decrease in SBP, respectively. Subgroup analyses demonstratedthat the association between SBP reductionand the decrease in plasma NMT (R=0.764, P=0.046) and NE (R=0.714, P=0.003) strengthens among patients with hypertension and among those with diabetes mellitus (R=0.974, P=0.026 for NMT).
Conclusions
SBP reduction during CST is associated with plasma NMT and NE decrease. Therefore, the decrease in SBP90 minutes post clonidine mayserve as an immediate complementary clinical tool for PPGLdiagnosis.

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AEP1009

Assessment of the awareness of cancer screening in patients with diabetes mellitus

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Objective
Cancer is an important public health problem. Cancer screening is effective method in fight against cancer. In addition to an increased risk for cancer incidence there is some evidence in the literature reporting that patients with diabetes have a lower rate of cancer screening and survival than non-diabetic patients. In this study, we aimed to assess the awareness of cancer screening programmes in diabetic patients who admitted to our outpatient clinic.
Materials and methods
This study was carried out using a questionnaire method as a cross-sectional case-controlled study to question cancer screening awareness in patients diagnosed with diabetes who admitted to the our outpatient clinic between September 2019 and February 2020. A poll including questions regarding age, gender, educational status, smoking/ alcohol use and whether they underwent any cancer screening programme was conducted to the patients who accepted to take part in the study.
Results
83 patients participated in this study. Sixty-seven (68.6%) of 83 patientswere female,16 (31.8%) of them were male. Among all patients, the proportion of patients who had all the recommended cancer screenings appropriate for their age was determined to be 3.3%. The average age of male patients was 57. And, the rates of male patients who underwent PSA measurement, colonoscopy, fecal occult blood test were 50.0%, 25.0% and 37.5%, respectively. The average age of women was 55. It was found that women diagnosed with diabetes complied the least with HPV testing, and the most with breast examinations, mammography and breast ultrasound. The rates of female patients who underwentHPV testing, colonoscopy, fecal occult blood testing, pap-smear, mammography /breast ultrasound and breast examination were 9.1%, 29.9%, 34.3%, 65.7%, 70.1% and 70.1%, respectively.
Conclusions
In our study, it was observed that the rates of participation in cancer screening in patients with diabetes were low. It is noteworthy that despite frequent admissions of diabetic patients to hospitals for routine controls, the rates of participation in cancer screening programmes are low. Informing diabetic patients about cancer screening programmes and encouraging them to undertake necessary screening tests during their controls may be effective in terms of early diagnosis and treatment modalities.

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AEP1010

Clinical presentation variations of pheochromocytomas

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Introduction
Pheochromocytoma (PCC) has a wide spectrum of clinical manifestations, from insidious disease to extreme symptoms. Various mechanisms of catecholamine and other mediators actions were related to the diversity of PCC presentation.
Aim
We describe a retrospective study, of patients with PCC from a tertiary hospital, focusing on clinical and biochemical characteristics of PCC depending on means of discovery.
Material and methods
Medical files of 67 consecutive patients diagnosed with pheochromocytoma between 1987–2018 were analysed in detail, collecting relevant clinical, hormonal and imaging data. The patients were divided in 2 groups: incidentaloma group (IG) with25 patients incidentally diagnosed with pheochromocytoma, upon imaging performed for reasons unrelated to a blood pressure abnormality or other pheochromocytoma related symptoms;symptomatic group (SG) included 42 patients diagnosed with pheochomocytoma after accusing pheochromocytoma related symptoms: arterial hypertension/hypertension paroxysms, headache, palpitation, sweating, anxiety.
Results
Mean age of diagnosis and tumor dimension were higher in incidentally discovered pheochromocytomas than in clinically suspected PCC (54.8±5.4 vs 44.0±12.2 years old respectively 5.2±2 vs 4.8±2 cm). There were no differences between gender distribution in IG, while in SG, women percentage was higher. As expected, a lower number of patients from IG had chronic hypertension (48%) or hypertension paroxysm (16%), while in SG, more than 90% of the patients reported either chronic hypertension or hypertension paroxysms. Other symptoms related to pheochromocytoma such as headache, palpitations or sweating were more intensive and more frequently reported in SG. Glicemic abnormalities were approximately equal distributed between the two groups. Arterial blood pressure normalization after surgery was reported in more patients from SG than in IG. 25 out of 31 hypertensive patients in SG had normalization of arterial blood pressure postsurgery, while 6 out of 12 hypertensive patients in IG had normal blood pressure after surgery.
Conclusion
Incidentally discovered PCCs are related to a more advanced stage of the disease (reported as higher tumor dimensions in our study) due to delayed time of the diagnosis. Incidentally discovered PCC are often asymptomatic; in half of the cases from our study, patients from IG had essential arterial hypertension rather than secondary hypertension. In case of an incidentaloma it is always required to screen for pheochromocytoma.

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AEP1011

A case of posaconazole associated adrenal insufficiency developing in the course of acute myeloid leukemia

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Posaconazole is a member of triazole antifungal family. It is frequently used prophylaxis and treatment in invasive fungal infections. Among the azole group antifungals, ketoconazole is well known to affect steroidogenesis through cytochrome P450 enzymes, however, posaconazole-induced adrenal insufficiency has been reported in only two cases in the literature. Here, we present our case of adrenal insufficiency induced by posaconazole.
A 54-year-old male applied to Hacettepe University Hospital with fever and weakness. The patient with anemia, leukocytosis, and thrombocytopenia was followed up with the diagnosis of standard-risk acute myeloid leukemia (AML). His history was beginning with acute retinal artery thrombosis ten years ago. The patient with JAK2V617F mutation was diagnosed with overlap of myelodysplastic syndrome/myeloproliferative neoplasm and followed up with supportive blood product replacement if necessary. Calcitriol treatment was started, who had primary hypoparathyroidism during follow-up. After four years of hypoparathyroidism, thrombosis was detected in multiple veins simultaneously with pulmonary thromboembolism and primary hypothyroidism, then hydroxyurea and levothyroxine were started. He had received posaconazole for invasive fungal infection during AML treatment. He has persistently hypoglycemia, hypothermia, hypotension18th day on posaconazole treatment. Sodium and potassium level 149 mEq/l, 3.4 mEq/l respectively, that day. We suggest that he had adrenal insufficiency, with appropriate clinical and laboratory features. After taking the tests for arterial blood gas, ACTH, cortisol, and blood culture, treatment for adrenal insufficiency was started. Cortisol 2 mg/dl, ACTH 75 pg/ml, testosterone < 13 ng/dl and DHEA-SO_4 21 mg/dl were observed in the blood sample taken at 6 PM. At the end of 12 hours, his clinical and laboratory response was dramatic. Sepsis is ruled out with this clinical and laboratory results, also no bacterial growth on the blood culture after five days. Posaconazole treatment was terminated, because it may cause adrenal insufficiency. In our patient, steroidogenesis appears to be affected as a whole under posaconazole treatment. He used steroid therapy for 45 days. His complaints did not recur during steroid dose reduction and after discontinuation of therapy. Together with the abdominal MRI and CT scans, which shows that adrenals were completely normal,and extensive iron accumulation on the liver, and we defined our patient as posaconazole-induced adrenal insufficiency on the background of hemochromatosis. We think that with the increase in prophylactic use of posaconazole, similar cases will increase. With the third case we present in the literature, clinicians should be careful in terms of adrenal insufficiency developed due to posaconazole use.

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AEP1012

Subclinical atherosclerosis is associated with anti-mullerian hormone levels in reproductively women

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Introduction
The prevalence of cardiovascular disease in reproductively active women has received limited attention. Recent data indicated possible adverse effect of non-typical obstetrical risk factors with regards to cardiovascular function. We aimed to evaluate the potential association between anti-mullerian hormone (AMH), a known marker of ovarian reserve, with subclinical atherosclerosis in young premenopausal women.
Methods
This was a cross-sectional study, comprising of 70 premenopausal women, aged 32.7 ± 6.5 years. Fasting blood samples were obtained to assess serum AMH levels as well as the lipid profile. Vascular studies were performed in one session and included indices of vascular structure (e.g. carotid and femoral intima media thickness, IMT) as well as vascular function (e.g. flow-mediated dilation; carotid-femoral pulse wave velocity, PWV).
Results
Serum levels of total cholesterol associated negatively with AMH concentrations. Moreover, smokers had lower levels of AMH when compared with non-smokers. Mean AMH levels associated inversely with carotid and femoral IMT values, in all of the assessed segments. The association between AMH concentrations and combined carotid IMT or carotid bulb IMT remained significant, even after multivariable adjustment for various established cardiovascular risk factors. No correlation was identified between AMH levels and indices of functional vascular disease or other markers of cardiovascular disease.
Conclusion
AMH levels are negatively and independently associated with indices of subclinical atherosclerosis as well as serum levels of total cholesterol, in this sample of young, health, normally ovulating women.

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AEP1013

A composite pheochromocytoma inneurofibromatosis type 1: A case report

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Introduction
The composite pheochromocytoma is a rare adrenal medullatumour that combines a pheochromocytome and a neuroblastic tumour. We present the case of a composite phenochromocytoma discovered in a patient with neurofibromatosis type 1.
Case report
Patient aged 64 years referred to our department by his dermatologist for the exploration of a left adrenal mass discovered during the practice of a CT scan and then an 18F-FDG MRImade as part of an exploration of his neurofibromatosis. The patient hada high blood pressure and neurofibromatosis type 1 for which he is followed since 1995 The radiological characteristics at the 18F-FDG MRIwas in favor of a moderately hyper-metabolic formation fixing to SUV max 3.1 of the left adrenal of 18 × 12 mm and then the Adrenal-centered scanner was in favor of a left adrenal nodule that has a spontaneous density, an absolute and relative wash against the diagnosis of adenoma. In biology we noticed a slight rise in urinary and plasma metadrenaline on two successive samples. The patient was operated (left adrenalectomy) because we consideredthe mass as a pheochromocytoma. He had simple surgical suites with the need to stop antihypertensive treatment. Anatomopathological examination was in favour of a composite phenochromocytoma with a ganglioneuroma with no sign of malignancy
Discussion
The largest series of composite pheochromocytoma studied was published by Gupta *et al.*, it included a single case of neurofibromatosis, the mean age atdiagnosis was 67years,and the average size was 5.2 cm. The majority were functionnaly activewith a moderate elevation of catecholamines. This published case is similar to our patient in clinical and biological characteristics.
Conclusion
Pheochromocytoma, as part of a neurofibromatosis, would have more specific characteristics that need to be better studied in order to refine the management of this chronic disease.

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AEP1014

Control of hypercorticism during paraneoplastic Cushing's syndrome secondary to atypical carcinoid tumor of the lung (about one case)

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Te paraneoplastic Cushing's syndrome represents 9 to 18% of ACTH-dependent endogenous hypercorticisms; which poses, in clinical practice, two types of problems:
– on the one hand, the differential diagnosis with Cushing's disease, when well differentiated and morphologically undetectable endocrine tumors are involved.
– on the other hand, the control of hypercortism, most often major in metastatic neuroendocrine tumors, which can in itself compromise the vital prognosis.
This is the case of our young patient, aged 26 years, who presents a Cushing's syndrome of rapid onset (after 4 months), marked by the intensity of the signs of hyperandrogenism with a severe hypokalemia of the order of 1.8 mEq/l, complicated by diabetes mellitus, hypertension and psychosis. Basal endocrine (ACTH: 905 pg/l, plasma cortisol: 2589 nmol/l) and pharmacodynamic (non-blocking with Dexamethasone) exploration, as well as non-visualization of a pituitary adenoma on hypothalamic-pituitary MRI, led us to favorize the diagnostic of hypercorticism by ectopic tumor secretion of ACTH. Thoracic CT scan found a right middle lobar lung tumor; an anapathological study of the bronchial biopsy, performed under bronchoscopy, revealed an atypical carcinoid tumor of the lung with mediastinal lymph node invasion. During the etiological investigation, and in view of the significant hypercorticism, anti-cortisol therapy was instituted, namely: LYSODREN* 2 gr/day per os, FLUCONAZOLE* 600 mg/day in IV, SANDOSTATINE* 400 mg/day subcutaneously, with weekly control of the renal, hepatic and lipid balance sheet. This therapy allowed a reduction of cortisol to more than 40% (1524 nmol/l) at D15 of treatment, allowing a normalization of hypokalemia resulting clinically in an attenuation of the signs of hyper androgenism and psychosis. The study of this case illustrates the characteristics of a paraneoplastic Cushing's syndrome indicative of a carcinoid lung tumor, and the usefulness of anti-cortisol therapy in the control of hypercorticism pending etiologic treatment.

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AEP1015

Primary adrenal insufficiency secondary to COVID-19 infection: A case report

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Introduction
Bilateral adrenal hemorrhage (BAH) is a rare clinical condition (estimated incidence between 0.14% –1.8%, according to postmortem studies) and life-threatening due to the development of adrenal crisis, after the destruction of 90% of each adrenal gland. A mortality rate of 15% has been reported despite treatment, but it depends on the severity of the underlying condition, reaching 90% in cases of sepsis, or even higher if it is not diagnosed quickly enough. Bilateral forms are common attributed to spasm or thrombosis of the adrenal vein. The main nontraumatic causes include

stressful situations, such as surgery, severe burns, or sepsis, bleeding diathesis (thrombocytopenia, anticoagulants therapies, especially in the setting of heparin-induced thrombocytopenia), thromboembolic disease (included antiphospholipid syndrome), adrenocorticotropic hormone (ACTH) hyperstimulation, and adrenal gland tumors, especially pheochromocytoma. The clinical suspicion of BAH is difficult because the clinical presentation is unspecific.
Case report
A 70-year-old man, with a medical history of prediabetes, went to the emergency department for presenting fever, asthenia, abdominal pain and cutaneomucosal hyperpigmentation for 15 days. Subsequently, he presented nausea, drowsiness and hemodynamic instability. The analysis reported lymphopenia, hyponatremia, hyperkalemia, elevated fibrinogen, PCR, ferritin, liver enzymes, LDH, D-dimer, and troponin-I. The cultures (blood and urine), conventional serologies and antiphospholipid antibodies were negative and the serology (IgM and IgG) for SARS-CoV-2 was positive. Imaging studies confirmed bilateral pneumonia, paralytic ileus and bilateral adrenal hemorrhage. He received hydroxychloroquine, azithromycin, thromboprophylaxis, intravenous fluid therapy, and hydrocortisone at stress doses. He was discharged at 7 days with hydrocortisone (20 mg/day) and fludrocortisone (0.1 mg/day).
Discussion
COVID-19 is a progressive endothelial thromboinflammatory syndrome, caused by the direct effects (cytokine storm, complement activation, extensive vascular deposition of C4d, C5b-9, MASP2 and fibrin) and the indirect effects of the infection (hypoxia, immobilization).Therefore, it is capable of causing vascular congestion and/or thrombosis of the adrenal vein, with the consequent increase in intraglandular pressure, collapse and adrenal bleeding.
Conclusion
There must be a high clinical suspicion of primary adrenal insufficiency in case of COVID-19 infection with abdominal pain, especially if it associates arterial hypotension refractory to fluid therapy, hyponatremia and hyperkalemia. Abdominal CT scan plays a crucial role in the confirmation diagnosis of BAH. If possible, ACTH and cortisol levels should be measured prior to corticosteroid therapy, without in any case delaying its administration. Replacement corticosteroid therapy should be started quickly.

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AEP1016

Clinical and hormonal features of the manifestation of various forms of congenital adrenal hyperplasia in children

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Medical History of thirty five patients aged from one to sixteen years diagnosed with CAH have been analyzed in the Republican Center for Pediatric Endocrinology. Among the thirty five patients participating in the study (boys–fifty seven percent, girls –forty-three) seventy-one percent is with salt wasting form (SWF), twenty-two percent with virilising form (VF), three percent with non-classical form (NF). The mean weight SDS at birth is minus eight hundredths ± one point seventeen, the mean height SDS is twelvehundredths ± one point six. Age of diagnosis SWF is seventeen point four ± sixteen point three days, VF is one point three hundredths ± four point six years. The most frequent signs of manifestation in SWF were regurgitation, body weight loss, vomiting, dry skin, hypotension, exicosis; in VF – premature pubarche. At the time of diagnosis, seventeen-hydroxyprogesterone (SOHP) was higher than normal range in all groups: SWF –eight hundredforty ± two hundred ninety-eightnmol/l, VF – three hundred eighty-six ± eighty-one nmol/l, NF –thirty-five nmol/l; increase morning values of adrenocorticotropic hormone (seventy-four ± two pg/ml). It was revealed that before treatment there were changes in electrolytes (K, Na) only in group with SWF (six point seven ± one point six mmol/l andone hundred twenty-six ± eleven mmol/l respectively). Blood glucose and pH in children with SWF were three point two ± one point forteen mmol/l and seven point three ± sixty-seven thousandths co-responsibly. All children received hydrocortisone replacement therapy at a starting dose of sixty-four ± twenty-eight mg/m^2 in SWF group; twenty-two ± twenty-one mg/square meter in VF group; twenty-one mg/m^2 in NF group. Patients with SWF additionally took fludrocortisone at a starting dose of seven hundred eighty-seven ± one hundred thirty-one mkg/square meter. Fourteen children from the total sample have reached puberty age. Height SDS is minus point four ± one point three, weight SDS one point thirteen ± one point thirty-three, BMI twenty-four point two ± three point six kg/square meter, SOHP –thirteen point fifty-six ± thirteen point forty seven nmol/l. Late diagnosis of the disease in patients was revealed regardless of the form of AH. Metabolic acidosis, hyponatremia and hyperkalemia, high level of SOHP are registered in the SWP group at the time of manifestation There were noted compensation of metabolic parameters, achievement of target growth indices, when children receive adequate replacement hormonal therapy.

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AEP1017

Clinical aging manifestations of cortisol secreting adrenal adenoma

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The objective was to study clinical aging peculiarities of manifestation period of cortisol secreting adrenal adenoma.
Materials and methods
Forty five patients with cortisol-secreting adrenal adenoma served the basis for the study. In that group of patients there were 11 (24.4%) men and 34 (75.6%) women, with the average age 27.5 ± 10.5 years old. Out of forty five patients 5 (11.2%) were children. All patients had common clinical, biochemical, hormonal, and instrumental tests.
Results
Cortisol-secreting adenoma were observed in young age from 18 to 44 years old (84.4%; $\chi^2 = 40.0$; $P < 0.0001$); according to gender distribution it was more often observed in women, than in men (75.6% vs 24.4% respectively). among children and people above 44 these tumors were registered less often, in 5 (11.2%) and 2 (4.4%) cases, respectively. Only 11 (24.4%) patients were diagnosed within one years from the start of the disease, 26 (57.8%) patients needed from 1 to 5 years for the diagnosis, and 6 (13.3%) patients were correctly diagnosed in 5–10 years, and that, certainly affected the results of treatment. Finally, two (4.4%) patients spent more than 10 years before they were diagnosed. The most characteristic manifestation of cortisol-secreting adenoma was arterial hypertension (AH) observed in 18 (40%) patients. Average age of the patients in manifestation period of AH was 25.3 ± 10.2 years old. We observed positive direct correlation between the age at the moment of AH debut and systolic AP ($r = 0.35$; $P = 0.03$). Sexual dysfunctions (10–22.2%) and weight gaining (13–28.9%) had similar prevalence at the debut of the disease. Less often the pathology started with stomachache and changes in appearance. In one case cortisol-secreting adenoma diagnosis was established when patient with acute disorder of cerebral circulation was checked after long-term neuropathologist's treatment of hypertonic disease. In the majority of cases when children suffered the disease its manifestations were non-specific, and displayed in weight gaining (100%), physical and mental retardation (60%), leading to the choice of observational strategy and absence of duly diagnostics and treatment.
Conclusion
Great number and variability of early clinical manifestations of cortisol-secreting adenoma cause difficulties in diagnostics reflected in the long duration of the disease, in other words time from appearance of initial symptoms till correct diagnosis. In children the basic symptom in manifestation of cortisol-secreting adenoma is gaining weight with no growth, which should urge pediatricians to perform targeted search for the disease.

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AEP1018

18 Flour-Cholin-PET-CTis the supreme tool to localize ultrasound and mibi-'negative' parathyroid adenomas – intraoperative correlation and 12 month postoperative results

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Background
To characterize the diagnostic performance of 18-Fluoroethylcholine-PET-CT (FCH-PET-CT) to localize parathyroid adenomas (PA) in primary hyperparathyroidism (pHPT) when ultrasound (US) and MIBI-Scan (MibiS) fail to localize – intraoperative correlation and one-year follow up.

Method
Beginning in 07/2017 18-FCH-PET was employed in patients with proven pHPT in whom US and MS delivered either incongruent or negative findings. All patients were offered cervical explorations with intraoperative PTH-monitoring (IO-PTH) and subjected to followed up for 12 months postoperatively.
Results
From 07/2017 to 05/2020 432 patients were operated for pHPT (17 redo-for-HPT, 62 with prior surgery to the neck). During this period 173 FCH-Pet-CTs were performed suggesting PA(s) in 162 (94%). 134 of the 173 patients of this cohort already had their surgery, confirming FCH to have accurately localized PA(s) to the respective side of the neck in 131; to have been false neg. in 2 and false pos. in 1, for a global sensitivity of 0.98; accuracy of 0.98 and PPV of 0.99. The 12-month postoperative follow up of the first 95 patients suggested that no PA(s) were missed. One patient with reoperative surgery because of persistent HPT may develop recurrent disease 10 months after surgery.
Conclusion
FCH-PET-CT is a clinically meaningful diagnostic utility when US and MibiS fail to localize a PA. FCH-PET-CT has the potential to replace MibiS. FCH-PET-CT allowes for planned unilateral and focused as opposed to bilateral explorations in almost all of our cases. We, therefore, suggest FCH-PET-CT for the localisation of negative PA(s).

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AEP1019

A global natural history study of Fibrodysplasia Ossificans Progressiva (FOP): 12-month outcomes

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Background
FOP is an ultra-rare, severely disabling genetic disorder characterised by cumulative heterotopic ossification (HO), often preceded by episodic flare-ups, leading to physical disability and early death. Initial misdiagnosis can occur in ~90% of individuals leading to unnecessary, often harmful interventions. FOP is diagnosed and managed by multiple specialists, including endocrinologists.
Objective
A prospective, 36-month, global natural history study (NCT02322255) was designed to investigate progression of FOP, HO, and impact on physical function. Results are described for the first 12 months.
Methods
Individuals with FOP aged ≤65 years with documented *ACVR1*^{R206H}mutation were eligible. HO volume was assessed by low-dose whole-body computed tomography (WBCT; excluding the head) interpreted at a blinded, central laboratory using pre-specified procedures. Physical function was evaluated using the Cumulative Analogue Joint Involvement Scale (CAJIS; total score 0–30 represents degree of ankylosis across 15 joints) and the FOP-Physical Function Questionnaire (FOP-PFQ; % total score); higher scores indicate more severe limitations. Changes from Baseline in HO volume, CAJIS and FOP-PFQ at Month 12 were evaluated.
Results
Of 114 participants with Baseline data, 99 (aged 4–56 years at enrolment, mean 17 years; 56% male) had a Month 12 assessment and 93 had evaluable WBCT HO data at Baseline and Month 12. Over 12 months, 40% (37/93) developed new HO and 48% (48/99) reported ≥1 flare-up. Of participants with new HO, 65% (24/37) reported≥1 flare-up (mean 2.3 flare-ups/year) and 35% (13/37) reported no flare-up. Of participants with no new HO, 43% (24/56) reported≥1 flare-up (mean 1.8 flare-ups/year). Among all participants, mean new HO volume in those who reported flare-ups was 39.718 mm^3 (SD: 91.969 mm^3; n=48) vs 5.081 mm^3 (S.D.: 14.582 mm^3; n=45) in those who did not. Mean changes from Baseline in CAJIS and FOP-PFQ were minimal (CAJIS: 0.6 [S.D.: 2.4; median: 1.0; n=99]; FOP-PFQ: 4.4% [S.D.: 11.2%; median: 3.7%; n=90]) and similar across participants with or without new HO.
Conclusions
In participants with FOP, WBCT HO volume increased over 12 months. Among those who experienced new HO, this was not preceded by a flare-up in over one third of cases. Among all participants, mean new HO volume in those who reported flare-ups was ~ 8 times higher than in those who did not. CAJIS and FOPPFQ were not sufficiently sensitive to assess disease progression over 12 months. Measuring HO may be a viable way to monitor changes in FOP over short periods of time.

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AEP1020

Elastographic techniques in localizing parathyroid adenomas

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Introduction
Primary hyperparathyroidism (PHPT) is the third most frequent endocrinopathy, after type 2 diabetes mellitus and thyroid disease. It is most commonly caused by an overactive parathyroid gland resulting in high serum parathormone (PTH) concentrations and consequent high serum calcium concentrations. PHPT is nowadays commonly asymptomatic, with high prevalence among postmenopausal women (female – male ration 3–4:1).
Materials and methods
We evaluated 20 consecutive patients diagnosed with primary hyperparathyroidism, from October 2018 to June 2019. All cases presented solitary parathyroid adenoma werecertified by pathology report after surgery (parathyroid adenoma excision). Pacients were evaluated clinically, biochemically and by ultrasound: 2 B ultrasound, Power Doppler, shear wave elastography with computer assisted quantitative measurement of tissue elasticity with high accuracy linear probe on Supersonic Aixplorer machine and strain elastography using Hitachi Preirus (Hitachi Medical Corporation, Tokyo, Japan) machine.
Results
We evaluated 20 consecutive patients (male to female ratio 1:19) with mean age of 57.3±13.33, mostly postmenopausal women with confirmed primary hyperparathyroidism. The parathyroid adenoma tissue was compared with the normal thyroid tissue and the surrounding muscle tissue. Using SWE elastography, we found that the mean SWE value for parathyroid adenoma is 4.74±2.745 kPa, compared to mean SWE of thyroid tissue 11.718±4.206 kPa, respectively muscle tissue 16.362±3.829 kPa. Parathyroid adenoma tissue was also evaluated with strain elastography with color maps (qualitative) and with strain ratio (semi-quantitave data). The initial qualitative analysis, found 15 out of 20 cases with score 1 on color map evaluation, according to Rago criteria. Semi-quantitative analysis using strain elastography, found a strain ratio of 1.46±1.45 for parathyroid/thyroid pair and 1.79±0.90 for parathyroid/muscle. Comparing the two elastographic methods, we have found that shear wave elastography method has a higher sensitivity and specificity, if parathyroid adenoma is compared with thyroid tissueor surrounding muscle – AUC curve 0.70, 95% CI [0.544; 0.876], compared with the specificity and sensitivity of strain elastography – AUC curve 0.646, 95% CI [0.442; 0.850].
Conclusion
To conclude, the aim of this prospective study was to quantify the value of strain elastography and 2D shear wave elastography in localizing parathyroid pathology. Although strain elastography can be a useful qualitative tool by using color mapping, 2D-SWE elastography can offer a better differentiation on tissue elasticity when diagnosing parathyroid adenomas. By using this elastographic technique, a value less than 7 kPa for mean elasticity index is suggestive for parathyroid adenoma.

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AEP1021

Association of osteoprotegerin 1181G>C and 245T>G polymorphisms and diabetic Charcot osteoarthropathy in Egyptian patients

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Aim
Egypt is among the world's top 10 countries in terms of the highest number of people with diabetes. Charcot foot is a serious complication that affect bones, joints, and soft tissues of the foot or ankle. Although the etiology is linked to different inflammatory markers, yet not clear. Recently, an association between two polymorphisms (1181G>C and 245T>G) of the osteoprotegerin (OPG) gene and Charcot was suggested. The aim of this study was to explore polymorphisms in the OPG gene and their possible contribution to the genetic susceptibility to Charcot neuro- osteoarthropathy (CNO) in Egyptian diabetic patients.
Methods
In this case-control study, in addition to history and clinical examination, Neuropathy was assessed by Neuropathy Symptom Score (NSS) and Neuropathy Disability score (NDS). MRI was done to acute charcot patients only to confirm the diagnosis. DNA was isolated OPG gene polymorphisms from 50 consecutive patients presented with CNO in addition to another 50 patients with diabetic neuropathy without CNO. A matched 50 healthy group of persons were also tested as control group. The collected data was revised, coded and tabulated using SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Logistic regression analyses was used for prediction of risk factors.
Results
It was found that rs2073618 gene, C allele is significantly associated with lower frequency in charcot group i.e. seems to have protective effect against CNO development. While the rs3134069 has shown no significant association in genotypes, alleles frequencies between diabetic cases with and without charcot groups.
Conclusion
The OPG gene polymorphisms seems to play a role in protection of diabetic Charcot neuro-osteoarthropathy in Egyptian diabetic patients. This was clear fromrs2073618 gene, C allele which proved to be associated with lower frequency of CNO.

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AEP1022

miRNAs regulating BDNF and BDNFas in adipose tissue: Potential link between obesity and mood disorders

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Background and aim
Obesity (Ob) is tightly associated with metabolic diseases such as type 2 diabetes (DT2) andinsulin resistance (IR). Furthermore, obesity has been identified as one of the primary causes of mood disorders (MDs) including depression. Several studies have demonstrated the link between Ob, adiposity, neuroinflammation and MDs. The Brain-Derived Neurotrophic Factor (BDNF) and its regulator, the non-coding RNA BDNF antisense RNA (*BDNFas)*, play an important role on the depression pathophysiology and therapeutic antidepressive mechanisms. However, the relation between BDNF and BDNFas, adipose tissue (AT) functionality and Ob has not yet been well defined. Preliminary, *in silico*analysis carried out by our grouphave shown that *BDNF* and *BDNFas* are validated target genes of miR-10a, miR-210, miR-182 and miR-27b. Thus, the aim of our study was to analyze the expression of these miRNAs, *BDNF*and *BDNFas* in human AT in Ob.
Materials and methods
miR-10a, miR-182, miR-210, miR-27, *BDNF* and *BDNFas* expression levels were measured by real-time qPCR from subcutaneous (SAT) and visceral (VAT) adipose tissue of normoweight subjects (NW, $n=9$) and metabolically healthy morbid obese (MHO, $n=9$).
Results
In this study, we observed that VAT miR-10a, miR-27b and *BDNFas* expression increased significantly in metabolically healthy obese subjects compared to NW individuals, while no significant changes were observed in miR-210 or *BDNF* expression. The expression levels of miR-10a, miR-27b, miR-210, *BDNF* and *BDNFas* in SAT were also higher in obese subjects compared to NW individuals. The correlative analysis has shown that the expression of miR-182 is positively correlated with *BDNFas* expression in VAT ($r=0.492$; P •0.05) whereas miR-210 expression is positively correlated with *BDNF* expression in SAT ($r=0.5089$; P •0.05).
Conclusion
Our results uncover new putative regulatory pathways involving miR-10a, miR-210, miR-182 and miR-27b in the control of the neuroinflammatory genes *BDNF* and *BDNFas* during obesity, and pave the way for future studies on the mechanisms which link obesity and mood disorders.
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AEP1023

Vitamin D status and its associations with clinical and laboratory parameters in patients with Addison's disease

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Introduction
The autoimmune process is currently the most common cause ofthe primary adrenal insufficiency cases in developed countries. The complexity of this process consists of genetic, immunological and environmental factors. It has been proven that vitamin D (VD) inhibits the production of inflammatory cytokines and can modulate immune-regulatory mechanisms.
Purpose
The aim of our study was to evaluate the prevalence of VD insufficiencyin patients with Addison's disease (AD), as well as to evaluate associations between vitamin D levels and the various clinical and laboratory parameters of the disease.
Methods
We retrospectively analysed medical records of 31 patients adults with the diagnosis of autoimmune Addison's disease and with measured serum VD levels. We analysed correlations between serum VD and various laboratory parameters as well as AD patients symptoms collected from structured medical interviews.
Results
90.3% of the subjects had inadequate VD level – 54.8% below 20 ng/ml and 35.5% between 20 to 30 ng/ml, respectively. Furthermore, 19.3% of patients have been found to be severely deficient in VD (<10 ng/ml). There were no significant associations of serum VD level with sex, age and smoking status.

There was a significant difference in VD level between patients previously supplementing and non-supplementing VD (23.91±3.6 vs 15.29±1.77 ng/ml, $P=0.02$). In 70% of patients who supplemented 2000 IU vitamin D prior to the admission to the hospital, supplementation did not provide adequate vitamin D level. Among various laboratory variables, only serum calcium levels significantly correlated with VD status ($r=0.53$, $P=0.006$). We observed that mean level of serum VD was significantly lower in patients with severe fatigue (15.17±8.41 vs 26.83±12.29 ng/ml, $P=0.011$) and limited exercise capacity (12.38±6.9 vs 21.63±10.87 ng/ml, $P=0.016$).No associations have been found between serum VD and other clinical features (fainting, loss of appetite, weight loss, nausea, vomiting, diarrhoea, musculoskeletal pain, abdominal pain).

Conclusion

This study demonstrates a high incidence of vitamin D deficiency and a significant correlation between low levels of VD and severe fatigue as well as limited exercise capacityin AD patients. Further studies are needed to clarify if impaired vitamin D level is a causal factor in the pathogenesis of AD andto assess if VD supplementation improves the quality of life of the AD patients.

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AEP1024

Severe hypercalcemia in infants, a report of three cases

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Introduction

Hypercalcemia in newborns and infants is often iatrogenic. Clinical signs are correlated with the degree of hypercalcemia and can lead to sever complications through dehydration, neurological disorders, convulsions and cardiac rythm disorders. The objective of our work is to study the clinical, biological, etiological and therapeutic aspects of hypercalcemia in infants.

Material and methods

Retrospective study on 3 patients hospitalized in our department in which we discovered hypercalcemia defined by a total calcemia > 2.7 mmol/l.

Results

We studied the cases of two girls and one boy. The average age at diagnosis was 3 months (40 days-6 months). The circumstances of discovery were: severe vomiting (1 case), weight loss (2 cases), polyuria with dehydration stage 3 (2 cases). Neurological disorders with hyporeactivity and irritability were objectified in all the patients. The ECG was normal in all cases. The mean blood calcium level was 3.84 mmol/l (3.2–5 mmol/l). Functional renal failure as well as recurrent and deep hypokalemia were found in the 3 cases. Stage II nephrocalcinosis was found in all 3 cases. The etiologies selected were: hypersensitivity to vitamin D in 2 cases (following a single dose of 200 000 IU of vitamin D), and vitamin intoxication in a case where the parents administered by mistake an excessive dose of vitamin D. The treatment consisted in an intravenous hyperhydration with the stop of the intake of vitamin D and calcium, furosemide (3 cases), corticotherapy (1 case), 3 courses of Pamidronate (1 case) and a cure of zoledronic acid (1case). The evolution was favorable in all cases with normalization of calcemia within 4 to 45 days.

Conclusion

Infant hypercalcemia can be evoked in the face of unspecific clinical signs and must be the subject of a rigorous diagnostic process with urgent management.

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AEP1025

Medications used by individuals with fibrodysplasia ossificans progressiva (FOP): Data from a global natural history study

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Background

FOP is an ultra-rare genetic disorder characterised by episodic progressive heterotopic ossification (HO) and flare-ups, causing cumulative disability and early death. FOP is diagnosed and managed by multiple specialists, including endocrinologists. There are no established disease-modifying therapies to prevent HO in FOP. Treatment guidelines for symptomatic relief of FOP have recently been published by the International Clinical Council on FOP (ICC).[1]

Objective

Report use of medications to manage FOP symptoms in a natural history study (NHS), as per standard clinical practice.

Methods

Individuals with FOP aged ≤65 years with a documented *ACVR1*^{R206H} mutation could participate in this 36-month, prospective, global NHS (NCT02322255). This analysis reports interim medication use data (cut-off: 31.08.2019). Use of medications (acute and chronic) was assessed at Baseline, by telephone at Weeks 1–3 and every 3 months thereafter, and at clinic visits (Months 12, 24 and 36). Medication prescribed for symptomatic treatment of reported flare-ups was recorded on flare-up Days 1, 42 and 84. Data were collected using a standardised list and are summarised here by preferred term (PT).

Results

73/114 (64.0%) participants had ongoing prior medications at Baseline; the most common by PT were prednisone (25.4%), ibuprofen (22.8%) and montelukast (19.3%), which are included in the ICC guidelines (Table). Pain relief medications ongoing at Baseline also included (among others): paracetamol (11.4%), naproxen (8.8%) and celecoxib (7.9%). Most participants (91/114; 79.8%) initiated treatment with new medications during the NHS; the most frequent were prednisone (31.6%), ibuprofen (28.1%) and paracetamol (21.9%). Glucocorticoids were commonly administered upon flare-up onset (155/217; 71.4%), in accordance with ICC guidelines.

Table 1 Use of medications included in the ICC FOP guidelines in the natural history study (NCT02322255).

	Ongoing prior medications at Baseline[a] *n*=114	Newly initiated medications *n*=114
Prednisone	25.4%	31.6%
Non-steroidal anti-inflammatory drugs		
Ibuprofen	22.8%	28.1%
Celecoxib	7.9%	3.5%
Indomethacin	3.5%	0.9%
Montelukast	19.3%	4.4%
Cromoglicate	5.3%	1.8%
Zoledronate	0.9%	–
Pamidronate	–	4.4%
Imatinib	–	1.8%

[a]Includes medications taken within 30 days prior to Baseline. FOP: fibrodysplasia ossificans progressiva; ICC: International Clinical Council on FOP.

Conclusions

To manage their symptoms during this NHS, individuals with FOP used various medications, which were generally consistent with current ICC guidelines. Although the study objective was not to evaluate efficacy or safety of medications used, it highlights the need for disease-modifying therapies to treat or prevent symptomatic progression of FOP.

Reference

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AEP1026

Anthropometric, metabolic and immunological parameters in children with type 1 diabetes mellitus and coexisting autoimmune disorders

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Objective
to assess the effects of associated autoimmune diseases on diabetes control, growth, lipid profile in children with type 1 diabetes mellitus (T1DM) and to determine the most predictive genetic, immune and metabolic risk factors of polyglandular autoimmunity in children with T1DM.
Material and methods
89 children with combined autoimmune pathology (main group, age 11.82±3.68 years) and 100 patients with isolated T1DM (control group, age 10.91±3.28 years) were recruited. Groups were comparable in age ($P=0.09$) and T1DM duration ($P=0.99$). Assessment of anthropometric parameters; biochemical blood parameters; glycosylated hemoglobin (HbA1c), vitamin D, thyroid hormones and antibodies to thyroid peroxidase (anti-TPO), to tissue transglutaminase IgA (tTGA) and to glutamate decarboxylase (GAD) levels was carried out. The assessment of height and body mass index (BMI) was carried out using the z-criterion (who, 2007).
Results
In the main group 42 children had combinations of T1DM with autoimmune thyroiditis (AIT), 15 - celiac disease (CD), 2 – Graves' disease, 3 – AIT and CD, 27 – elevated anti-TPO-antibodies. BMI and height z-scores in both groups corresponded to the mean age values and didn't differ significantly ($P=0.47$ and 0.28 respectively). HbA1c level in children with combined autoimmune pathology was higher than in the control group (7.99±1.74% vs 7.49±1.30%, $P=0.029$). Both groups demonstrated similar values of biochemical blood parameters: lipidogram, serum iron, and ferritin ($P>0.05$). Higher levels of anti-TPO antibodies were revealed in the main group (253.08±308.06 IU/ml) compared to the control group (32.07±28.83 IU/ml, $P=0.003$). Among the risk factors for autoimmune thyroid damage, the association of thyroid pathology with vitamin D deficiency has been established ($\chi^2=4.79$, $P=0.029$, odds ratio (OR) 3.23, 95% confidence interval (CI) 1.10–10.46). Tendency to a higher risk in female patients (OR 1.64, CI 0.87–3.12), and with a high levels of GAD antibodies (OR 2.00, CI 0.89–10.52) was detected. The analysis of risk factors for CD revealed a tendency to an increased risk in patients with autoimmune thyroid disease (OR 1.463 (CI 0.606–3.530)), elevated levels of GAD (OR 2.514 (CI 0.892–7.085)). There was no association of CD risk with age of manifestation and duration of T1DM.
Conclusions
1. Higher levels of HbA1c were detected in children with polyglandular autoimmune pathology.
2. Higher risk of autoimmune thyroid disease was found in patients with vitamin D deficiency. Potential risk factors for thyroid pathology include high levels of GAD antibodies, presence of gluten enteropathy, female gender and late puberty, and for CD – high levels of GAD antibodies.

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AEP1027

Utilising internet of things and artificial intelligence to enable twin precision treatment for reversal of type 2 Diabetes

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Introduction
We evaluated Twin Precision Treatment (TPT) approach, a cluster of Internet of Things (IoT) and Artificial Intelligence (AI), validated biosensors and Continuous Glucose Monitoring (CGM) through Ambulatory Glucose Profile (AGP) integrated with machine learning algorithms, enabling physicians to empower patients to reverse diabetes.
Methods
64 T2DM (19 males, 45 female), registered on Twin Health TM service, managed by standard care of approach with TPT, were monitored for three months for change in glycemic and non-glycemic parameters with changed pharmacotherapeutic approach. Patients achieving HbA1c >6.5% and ≤6.5 were classified as responders (RG) – demonstrating reversal of diabetes and non-responders (NRG), respectively. Twin Platform was used to correlate and analyse billions of data points to understand the drivers of the glucose response to specific foods for each participant. ANOVA was utilised for statistical analysis.
Results
The mean duration diabetes was 7 years (95% CI 0.1 to 30.0), with mean duration in the RG ($n=25$) was 4 years (95% 0.1 to 15.0) as compared to the mean duration of diabetes in NRG ($n=39$) was 10 years (95% CI 0.1 to 30.0); ($P=0.009$). The rates of diabetes reversal were 10%, 75% and 41% in HbA1c tertiles of HbA1c of >9.5, 8.1–9.5, 6.5–8, respectively. HbA1c reduced by 1.9 (8.8±2.23 to 6.9±1.07) ($P<0.001$). There was non-significant, but numerically superior improvement in non glycemic parameters in the RG Vs NRG with body weight reduced by 5.8 kg to 79.7±15.90, SBP by 8.68 mmHg to 122.92±10.06. In RG, C-peptide, LBGI (Low Blood Glucose Index), FPG, and HOMA-IR decreased by 0.71 ng/ml to 1.97, 1.19 to 0.67, 21 mg/dl to 112.4, 4.26 to 3.04, respectively. Glucose Variability of patients was maintained at 17%. 45 out of 57 patients who were on at least one anti-diabetic medication at baseline, were off the medication.
Conclusion
Technology enabled precision nutrition, a combination of macro, micro and biota nutrients, along with serial HbA1c evaluation are key for reversal of diabetes. Physician enabled adoption and integration of the technology, empowers patients to achieve better glycemic control. Our study with limited dataset with short duration validates robustness of TPT approach for a precise and effective metabolic control beyond hyperglycaemia.

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AEP1028

A call for cardiologists and diabetologists to embrace neurological investigation for diabetic neuropathy in cardiovascular risk stratification

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Background
In the 2019 ESC Guidelines on diabetes, pre-diabetes and cardiovascular diseases, only retinopathy appears as a target organ damage as a parameter for stratification patients into very high-risk group. The aim of study was to check the strength of association between DN and isolated DR groups with cardiovascular complications.
Methods
Chronic kidney disease (CKD) was defined by eGFR ≤59 ml/min/1.73 m^2 and proteinuria (PrU) was determined (mg/24 h). Neuropathy was diagnosed by neuropathy disability score and sudomotor function using Neuropad. Presence of coronary artery disease (CAD) and cervico-cerebral ischaemic aterial disease (CCAD) was documented. Lower-extremity artery disease (LEAD) was diagnosed with ankle-brachial index (ABI) and continuous wave Doppler.
Results
Of 262 people, 49.6% were male and 71% had T2DM; 130 had DN [90 (69.2%) with retinopathy], 75 had DR without neuropathy, 57 had no evidence of retinopathy, CKD and DN (controls). All ($n=48$) CKD patients were with DR and/or DN: 15 (31.3%) with DR, 10 (20.8%) with DN, 23 (47.9%) with both DN and DR. Patients with DN compared with controls after multivariable logistic regression analysis (MVLR) significant remained model: age (OR 1.16 [95% CI : 1.07–1.25]; $P<0.01$), duration of diabetes (1.12 [1.05–1.19]; $P<0.01$), PrU (1.003 [1.00–1.005]; $P=0.06$), NeuroPad time 1.11 [1.00–1.22]; $P=0.04$). Compared with controls, those with DR were more frequently women (62.7% vs 42.1%; $P=0.01$) and older (54.8±14.6 vs 45±12.8 years; $P<0.01$), had high blood pressure (49.3% vs 26.3%; $P<0.01$), T2DM (69.3% vs 43.9%; $P<0.01$), had longer duration of diabetes (17.1±7.7 vs 10.2±7.4 y.; $P<0.01$).After MVLR only duration of diabetes (OR 1.12 [1.05–1.19]; $P<0.01$) persisted. DN group was significantly more associated with macrovascular complications (CCAD, CAD, LEAD) [$n=56$ (43.1%)] vs DR group $n=16$ (21.3%) and control group $n=9$ (15.5%); $P<0.01$. CAD ($n=43$) in univariate analysis showed association with DN (OR 2.4 [1.2–4.8]; $P=0.01$), and in MVLR anaylsis with LEAD (OR 3.4 [1.6–7.1]; $P\leq0.01$).

Conclusion
In the algorithm for cardiovascular risk stratificationwe would recommend examination of diabetic neuropathy and LEAD as the first line approach. As earlier these complications would be detected the indication for more comprehensive management of diabetic patients would be established.

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AEP1029

EndogenousInterleukin production by the skin cells (keratinocytes and fibroblasts) cocultured with mononuclears of patients with type 2 diabetes mellitusand type 2 diabetes with chronic foot ulcers in a 3D culture model

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Our research focused on the role of immune mechanisms in diabetic foot ulcers development and impaired healing. The AIM of this study was to evaluate endogenous interleukin (IL1,4,6,8) production to the culture medium by the skin cells (keratinocytes and fibroblasts) cocultured with mononuclears of patients with type 2 diabetes mellitus (T2DM) and T2DM with chronic foot ulcers (DFU) in a 3D culture model.
Materials and methods
A multilayer 3D immunocompetent model of human skin comprising of keratinocytes, fibroblasts and mononuclears (peripheral blood mononuclears of 9 T2DM with DFU, 9 T2DM patients, 9 healthy controls (HC)) in an agarose-fibronectin gel was used. IL1,4,6,8 production to the culture medium was evaluated just after adding mononuclears to the system and in 24 hours of their co-cultivation with fibroblasts and keratinocytes.
Results
the initial IL1 level was significantly higher for samples with T2DM and T2DM with DFU patients mononuclears compared to HC – 54.91 [51.17;62.98] vs 51.82 [48.43; 55.92] vs 44.72 [35.37; 48.03] pg/ml, H=10.427, P=0.005. There was a significant increase in IL1 after 24-hour keratinocytes and fibroblasts coincubation with patients mononuclears – 48.91 [39.66; 51.96] vs 44.72 [35.37; 48.03] pg/ml, T=–2.666, P=0.008, 73.95 [68.13; 75.53] vs 51.82 [48.43; 55.92] pg/ml, T=–2.666, P=0.008, 85.17 [82.99; 91.51] vs 54.91 [51.17; 62.98] pg/ml, T=–2.666, P=0.008, for HC, T2DM and T2DM with DFU in 24 hours and initially, respectively. For the samples containing HC mononuclears this increase in IL1 was significantly lower than for T2DM and T2DM with DFU – 4.24 [3.65; 5.01] vs 20.21 [18.18; 23.51] vs 30.26 [26.62; 34.95] pg/ml, H=22.317, P<0.001, respectively. The increase in IL1 was significantly higher for samples with mononuclears of patients with T2DM with DFU, than without DFU – P<0.001. The initial IL6 level was slightly higher for samples with patients with T2DM and T2DM with DFU mononuclears than HC – 26.28 [20.82; 28.49] vs 27.54 [24.33; 30.03] vs 19.75 [13.57; 25.03] pg/ml, H=8.892, P=0.012, respectively. In samples with HC mononuclears, the IL6 was undetectable with the kits used (< 5 pg/ml). In the samples with patients with T2DM and T2DM with DFU mononuclears the secretion of IL6 didn't change significantly – 26.28 [20.82; 28.49] vs 23.76 [22.38; 27.58] pg/ml, T=–1.125, P=0.260 and 27.54 [24.33; 30.03] vs 26.12 [23.64; 28.90] pg/ml, T=–1.836, P=0.066 for the group of T2DM and T2DM with DFU initially and in 24-hour coincubation, respectively. The IL4 and IL8 levels were undetectable (<5 pg/ml) with the kits used.
Conclusion
An increase in IL1 and absence of a sufficient and significant decrease in IL6 production in 24-hour coincubation of skin cells with T2DM patients mononuclears indicates the activation of immune mechanisms and the maintenance of chronic inflammatory response.

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AEP1030

Variants of hyperlipidemia in obese children are gender and insulin resistance dependent

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Background
Insulin resistance and dyslipidemia inobese subjectsare important for predicting future cardiovascular risk. Purpose of the study was to analyze the lipid profile of obese children depending on gender and insulin resistance status.
Subjects and methods
247 overweight and obese children (160 boys and 87 girls) aged 2 to 18 y.o. were examined in the pediatric endocrinology department. Lipids assessment included measurement of total cholesterol (TC), triglycerides (TG), low density lipoproteins (LDL), high density lipoproteins (HDL).To evaluate lipid parameters, we used recommendations of the NCEP, 2006. For assessing carbohydrates fasting blood glucose and insulin levels were measured followed by HOMA-IR calculation. Insulin resistance was determined if HOMA-IR values exceededIDEFICS charts cut-offs. Parameters were grouped by the presence (IR +) or absence (IR-) of insulin resistance. Fasting status (at least 8 hours) was required. Standard statistics used for the data analysis.
Results
Insulin resistance was detected in 69.9% of overweight children. 72% of the examined girls and 68% of the examined boys were insulin resistant.
TC level in the IR+was at borderline levels in boys (4.43 mmol/l) and in girls (4.98 mmol/l), but in girls the level was significantly higher (P=0.03). In IR- subjects TC level was within normal limits in both boys (4.38 mmol/l) and girls (4.24 mmol/l) without gender difference. TC level was higher in girls with present IR (4.98 vs 4.24 mmol/l, P<0.05). In boys, there was no significant difference. Elevated TGs were found in boys (1.54 mmol/l) and girls (1.81 mmol/l) in the IR+group, as well as in girls from the IR- group (1.63 mmol/l). TGs in IR- boys were borderline and lower than in IR +group (1.30 vs 1.54 mmol/l, P<0.05). Whereas in girls there were no significant differences. HDLs were slightly reduced in all study groups. However, HDL level was significantly lower in boys without insulin resistancethan in girls (1.11 mmol/l vs1.37 mmol/l, P=0.03). There was no deviation of LDL from references in all groups regardless of gender and the presence of insulin resistance. Meantime, average LDL level was higher in insulin resistant boys than insulin sensitive ones (2.26 vs 1.72 mmol/l, P <0.05). IR girls also had higher LDLs than insulin sensitive (2.64 vs 1.63 mmol/l, P <0.05).
Conclusions
Most of obese and overweight children are insulin resistant with deteriorated lipids. Seems, variant and degree of dyslipidemia are gender and insulin sensitivity dependent.

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AEP1031

Type 2 diabetics with high risk of foot amputation: Role of sodium-glucose co-transporter inhibitors

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Introduction
The use of iSGLT2 continues to be controversial in diabetic patients with peripheral arterial disease.
Objectives
Assess the metabolic effect and the risk of amputations of iSGLT2 in diabetic patients cared for in the Multidisciplinary Diabetic Foot Unit (MDFU) compared to a control group.
Material and methods
A retrospective observational study where patients attended at the MDFU from December 2017 to January 2020 were recruited. An iSGLT2 treatment group was selected and these data were compared with a control group. Clinical, metabolic, anthropometric variables and amputation rate were collected in both arms. Statistical analysis was performed using the SPSS program (SPSS, inc, v15.0).
Results
A total of 312 patients were recruited: 83 in treatment with iSGLT2 and 229 as a control group. The treatment group had a mean age of 65.99±10.31 vs 68.14±12.11 (P=0.12) years of the control group and a time of evolution of the disease of 17.33±10.26 vs 18.10±11.97 (P=0.52). Weight of 86.88±17.77 kg vs 82.65±15.65 kg (P=0.57) and a mean BMI 31.07±5.61 kg/m^2 vs 29.58±4.91 kg/m^2 (P= 0.03). HbA1c at baseline (iSGLT2 vs control group): 8.83±1.67% vs 7.71±1.72% (P=0.00); mean reduction: 1.04±1.32% vs 1.42±2.34% (P=0.38); Final HbA1c: 8.08±1.37 vs 7.42±1.32% (P=0.05). There were no statistically significant differences between the LDL values at baseline (96.29±38.95 mg/dl vs

98.8±40.93 mg/dl, $P=0.67$)) or between the reductions obtained in both arms (11.28±31.16 vs 12.25±31.84, $P=0.91$). Taking into account some risk factors for an amputation to occur, there was a higher proportion of hypertension (78.3% vs 72.2%), dyslipemia (74.7 vs 71.1%), smokers (58.2 vs 49.8%) in the group with iSGLT2, as well as a longer history of chronic ischemia (41 vs 38.2%) and neuropathy (74.4 vs 70.9%). The amputation rate after follow-up was 15.7% in the iSGLT2 group compared to the control group 12.3% ($P=0.55$).

Conclusions

This study shows that the treatment with iSGLT2 in a group of patients with peripheral arterial disease is effective and safe, not increasing the rate of amputations compared to the rest of the patients attended in the MDFU, despite having a higher number of risk factors for this.

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AEP1032

Association between variants in clock genes and type 2 diabetes in an elderly greek population

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Background

Recent data suggest that disturbances in circadian clock functioning are implicated in the pathogenesis of type 2 diabetes (T2D), through alterations in plasma glucose levels, insulin secretion and sensitivity, energy intake, and genomic expression in liver and pancreas. This study aimed to assess a potential association between variants in clock genes and T2D risk in a population of Greek elderly people.

Methods

In a case-control design, 1258 participants aged 65 and above, were categorized either as T2D patients (Group A, $n=716$) according to diabetes history, HbA1c≥6.5% and fasting plasma glucose (FPG)≥126 mg/dl, or non-diabetic controls (Group B, $n=569$). Informed consent was obtained from participants and whole blood was collected for DNA extraction. Samples were analyzed on Illumina Infinium PsychArray. After individual and SNP quality control, polymorphisms in PPARA, PPARD, PKDREJ, UTS2, CLOCK/TMEM165, VAMP2, HES6 and PER2 genes were selected and allele frequencies between groups were compared (primary analysis). For the purpose of the compound analysis, the PLINK software suite (v1.9) was used. Permutation test analysis was implemented to determine statistical significance ($P<0.05$). In order to eliminate the impact of prediabetes on the results, participants from Group B with HbA1c levels<5.7% and FPG<100 mg/dl were selected to form a control subgroup (Group $n=393$) and a secondary analysis was undertaken.

Results

In the primary analysis, a protective effect of 14 *PPARA*variants against T2D was established. A similar trend was evident for rs7291444_G/T ($P_{emp}=0.031$, OR=0.7843), rs36125344_C/G ($P_{emp}=0.043$, OR=0.758) and rs6008384_C/T ($P_{emp}=0.036$, OR=0.798) in *PKDREJ*, in both primary and secondary analyses. Interestingly, rs6744132_A/G, located downstream *HES6* and *PER2* genes was positively associated with T2D ($P_{emp}=0.044$, OR=1.183). rs2859389 in *UTS2* gene was found to be protective against T2D ($P_{emp}=0.046$, OR=0.8454). Only in the secondary analysis, rs2278637_G/T ($P_{emp}=0.015$, OR=0.784) in *VAMP2* and rs11943456 ($P_{emp}=0.018$, OR=0.787) in *TMEM165* exhibited a protective role against T2D.

Conclusion

Our data indicate a potential role of variation in clock genes in T2D genetic susceptibility in an elderly Greek population. Further studies are required to replicate our findings and clarify the complex underlying interactions between genetic, environmental and life-style components that result in the development of the disorder.

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AEP1033

Prolonged Metformin intake is associated with decreased thyroid nodular growth in obese

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Obesity and weight excess is a widespread condition all over the world, as well as thyroid nodular disease. Screening studies in different populations prove a higher frequency of nodular thyroid formations of various nature in overweight individuals.

Aim

In our study, we evaluated the dynamics of the volume of dominant and non-dominant nodular formations, as well as their sonographic structure in overweight patients with prediabetes in the groups with two-year administration of Metformin and without.

Materials and methods

We have screened 550 patients in rural areas of Belarus. Anthropometry, Endocrinologists examination, thyroid ultrasound and serum blood tests were performed. Of the screened cohort there were 183 persons with BMI over 27 kg/m^2 associated with thyroid nodules who agreed to participate with informed consent. All cases of thyroid malignancy, thyrotoxicosis, Hashimoto thyroiditis and severe hypothyroidism were excluded from recruitment. Initial consultation with the proposal of individual weight-loss, nutrition and physical activity program was made for all participants. Additionally, those, who had metabolic reasons, glucose intolerance, dislipidemia – were prescribed Metformin in the dose of 1000–2550 mg/day. Two groups were formed – Overweight with thyroid nodules ('OWTN') and Overweight with thyroid nodules and Metformin intake ('MFI'). The groups were comparable by age, BMI, metabolic characteristics and thyroid status.

Results

As a result of 2 year follow up we have observed improvement in metabolic parameters of the MFI-group, showing improved glycaemic and lipid profiles, compared to OWTN-group. But we have detected a significant increase in number and volume of thyroid nodules in OWTN-group up to 1.84±1.47 ml, comparing to 1.37±0.99 ml in the MFI-group ($P=0.0399$), with a non-significant weight reduction, in between groups. As for thyroid status – there was also a significant difference in TSH (3.94±1.0 vs 2.89±0.7, $P<0.001$) and FT4 levels (16.22±2.48 vs 16.98±2.05, $P=0.027$) accordingly.

Conclusion

The obtained results of dynamic observation indicate a significantly less active increase in the volume of nodular formations in the cases of prolonged use of Metformin. Possible mechanisms of Metformin-induced PPAR-g receptor activation and additional effects of improved insulin sensitivity as well as Metformin direct influence on TSH-receptor affinity and activity for controlling neoplastic processes and thyrocyte proliferation are discussed. Larger number cohort and prolonged observation are still desirable.

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AEP1034

Characterization of dyslipidaemia and association of lipoprotein(A) plasma levels with metabolic control in young adults with type 1 diabetes

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Introduction

The 2019 European Society of Cardiology/European Atherosclerosis Society lipid guidelines changed the cardiovascular risk categories and LDL-C goals, and suggests that lipoprotein(a) [Lp(a)] measurement should be considered at least once in adult person's lifetime. Although young people with type 1 diabetes (T1DM) without major cardiovascular risk factors (CVRF) were previously considered to be at low or moderate risk, they are at least at

moderate risk based on the best available evidence. Emerging studies suggest that increased Lp(a) levels are associated with poor metabolic control in patients with T1DM. However, the knowledge about Lp(a) in T1DM is still limited.
Objectives
To evaluate the application of these guidelines and to investigate the association of Lp(a) and metabolic control in young adults with T1DM.
Methods
Observational cross-sectional study, including young adults (18–40 years) with T1DM. Patients with Lp(a) measurements were divided into two groups: very low-intermediate Lp(a) levels (≤120) vs high (>120 nmol/l).
Results
Included 75 T1DM patients (61.3% male), with median age of 30.9 (26.0–36.0) years, T1DM duration of 13.0 (6.0–20.0) years and HbA1c 7.7 (7.1–8.8)%. Median LDL-C was 105.0 (85.0–128.0) mg/dl. Among 9/75 (12.0%) patients at moderate risk (T1DM aged <35 and T1DM duration <10 years, without other CVRF), 1 (11.1%) had LDL-C above the target (≥100 mg/dl). Of the 44/75 (58.7%) at high risk (DM ≥10 years, without target organ damage or another CVRF), 38 (86.4%) had LDL-C ≥70 mg/dl. Among 22/75 (29.3%) patients at very high risk [DM with target organ damage, at least 3 major CVRF or early onset of T1DM of long duration (> 20 years)], all were above LDL-C goal (≥55 mg/dl). Median Lp(a) was 17.0 (6.0–39.0) nmol/l (n=54), no patients had extremely high levels (>430 nmol/l). Among patients not treated with antidyslipidemics, 3/48 (6.3%) had high Lp(a) levels [all at high risk and with LDL-C above the recommended goal (≥70 mg/dl)]. Patients with high Lp(a) levels had significantly higher body mass index (P=0.042), high-sensitivity C-reactive protein (P=0.041), total cholesterol (P=0.014), LDL-C (P=0.002) and non-HDL-C (P=0.003); and a trend to higher HbA1c and apolipoprotein B/AI ratio (both P=0.054). Lp(a) levels did not differ according to metabolic control (HbA1c <6.9 vs ≥6.9%). By the logistic regression method, none of the studied variables was predictive of high Lp(a) levels.
Conclusion
This study suggests that Lp(a) is a high risk marker in young adults with T1DM. Routine Lp(a) measurement in clinical practice could improve their cardiovascular risk assessment and justify intensive treatment.

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AEP1035

Polygenic risk scorecaptures 11% of of type 2 diabetes variability in latvian population

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Type 2 diabetes (T2D) is a multi factorial disease with increased prevalence globally. The risk of developing T2D is determined by the interaction of genetic and environmental factors. Over the decades of research, hundreds of T2D genetic susceptibility markers (mostly single nucleotide polymorphisms or SNP) have been discovered. Yet generally their contribution to increased T2D risk is small and have negligible value in clinical practice to aid T2D treatment, categorize patients or guide prognosis. To overcome the weakness of individual genetic markers, polygenic risk score (PRS) method has been developed to account for genetic background of an individual and presence of multiple T2D risk markers. T2D associated SNPs vary across populations and countries which translate into even higher heterogeneity of a PRS model. Therefore, it is important to develop PRS model for each country and population. This study performed a genome wide association study in Latvian population using 822 cases and 802 controls and developed a PRS model to capture genetic risk of T2D in Latvian population. The results indicate that seven SNPs have a statistically significant association with T2D in Latvian population after Benjamini-Hochberg false discovery rate correction and considering population stratification and other covariates. The overall correlation of effects of SNPs with recent report in meta-analysis of European populations (Mahajan 2018) is high, reaching r=0.39 when considering SNPs up to $P=1\times10^{-2}$. PRS model included 41 independent SNPs and contributes to 12% variability of T2D in the target group and 11% in the validation group with $P=1\times10^{-7}$ and AUC 0.69. Upper quartile individuals have T2D odds ratio 2.8 (CI 95% = 1.3–5.7) while lower quartile has odds ratio 0.3 (CI 95% = 0.3–0.7) when compared to the second quartile. Heritability of T2D has been determined at 26% in populations of European descent, therefore, capture of 11% variability translates to 42% of inherited variation explained in Latvian population by current PRS model. Many of the established T2D genetic risk factors were statistically significant (such as TCF7L2 gene) but failed to reach genome wide significance after correction for multiple testing, indicating that study is undepowered and larger sample size is required to improve detection of individual SNP effects and to improve PRS model. This T2D study has produced a strong PRS model explaining 11% of the diabetes variability in Latvian population and could be used in analysis with other T2D risk factors.

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AEP1036

Insights on ghrelin immunohistochemistry: Variations between intrinsic molecular subtypes of breast cancers

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Introduction
Ghrelin, a peptide hormone produced in the stomach, stimulates secretion of growth hormone and regulates appetite and energy homeostasis. Various other effects attributed to ghrelin may contribute to many aspects of cancer development and progression.
Material and methods
Using polyclonal antibody immunohistochemistry, we assessed (by intensity scoring) the immunolocalization of ghrelin in 70 tissue samples, and described particularities within the molecular subtypes of breast cancer. Clinical and histopathological characteristics of the tumors were obtained from patients' records. Patients histological data was grouped in order to better classify the ghrelin staining characteristics and included primary tumor size (≤ 20 mm; >20 mm), lymph node invasion (with; without confirmed lymph node invasion), tumor grading, estrogen (ER) and progesterone (PgR) receptor percentage score, intensity score and status (<1%; >1% positive in tumor cells), human epidermal growth factor receptor 2 (HER2/neu) status (positive; negative or equivocal), Ki-67 index (<15%; ≥15%) and presence of fibrocystic breast disease.
Results
Ghrelin expression in breast tumor cells correlated inversely with tumor grading (ρ = –0.449, P=0.020), and positively with estrogen receptor (ER percentage scoring, ρ = 0.221, P=0.003). Dividing the study group by intrinsic subtypes, a strongly inversely association between ghrelin and tumor size (P=–0.598, P=0.007), grading (P=–0.849, P=0.003), and presence of fibrocystic breast disease (P=–0.826, P=0.033) was observed in triple negative breast cancer cases. Tumor ghrelin and ER percentage scores were positively correlated in luminal B HER2 negative tumors (ρ = 0.121, P=0.031). For luminal A tumors, a negative association was observed between ghrelin and tumor grading (ρ = –0.364, P=0.656), lymph node status (ρ = –0.230, P=0.232), ER (ρ = –0.363, P=0.188) and PgR (ρ = –0.313, P=0.241) status, Ki67 index (ρ = –0.489, P=0.087) and the presence of fibrocystic breast disease (ρ = –0.224, P=0.656), associations whichdid not reach the level of statistically significance in any of these cases.
Conclusion
Ghrelin regulates several endocrine functions with potential contributions to cancer biology. An endocrine effect of ghrelin, potentially attributable to cancer biology, is its stimulation of growth hormone secretion regulating IGF-1 levels, with subsequent pro-neoplastic effects. However, existing evidence does not strongly support contribution of ghrelin-GH-IGF1 axis to cancer development or progression, but rather prove independent effects. Previous cohort studies reported a positive prognostic significance of ghrelin immunostainings in breast cancer. Furthermore, we showed that ghrelin was linked to better tumor differentiation and proliferation especially in triple negative cases, suggesting a particular mechanism of action and a possible prognostic role of ghrelin in these cases.

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AEP1037

Management of glucose profile throughout strict COVID-19 lockdown by patients with type 1 Diabetes prone to hypoglycemia using sensor-augmented pump

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Aims
Spain has been one of the worst affected countries by the COVID-19 pandemic. A very strict lockdown at home was imposed with a tough restriction of mobility. We aimed to evaluate the impact of this exceptional scenario on glucose profile of patients with type 1 diabetes (T1D) prone to hypoglycemia using sensor-augmented pump (SAP).
Methods
Patients with T1D prone to hypoglycemia using SAP (640G Medtronic Minimed) for at least 6 months under the funding of a National Health Service were included in an observational, retrospective study. Data were collected in two periods: pre-lockdown (PL), February 23rd–March 7th and within lockdown (WL), April 1st to 14th 2020. The primary outcome was the difference in the proportion of time in target glucose range of 70–180 mg/dl (TIR). Additional glucometric data and total daily insulin were also analysed.
Results
59 patients were included: 33 women, age 46.17 ± 13.0 years and disease duration of 30.2 ± 12.0 years. TIR 70–180 mg/dl (67.6 ± 11.8 vs 69.8 ± 12.0%), time > 180 (28.1 ± 13.6 vs 25.5 ± 13.1%), time > 250 (6.9 ± 6.1 vs 5.1 ± 4.8) and Glucose Management Indicator (GMI) (6.94 ± 0.8 vs 6.75 ± 0.7%) significantly improved (PL vs WL, respectively, $P < 0.05$). Time in hypoglycemia, coefficient of variation, sensor usage and total daily insulin dose remained unchanged.
Conclusions
Lockdown conditions imposed by the COVID-19 pandemic may be managed successfully in terms of glycemic control by population with DT1 prone to hypoglycemia using SAP. The strict daily routine at home could probably explain the improvement in the time in glycemic target without increasing the time hypoglycemia.

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AEP1038

Gestational diabetes as unusual presentation of maternally inherited diabetes and deafness (MIDD)

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Maternally inherited diabetes and deafness (MIDD) is rare subtype and monogenic form of adult onset diabetes caused from point mutation at position 3243 of mitochondrial DNA. The name indicates the main features of disease including diabetes and sensorineural hearing loss. About one percent of people with diabetes can have MIDD but the diagnosis can be challenging and needs high clinical suspicion on basis of family history, clinical features of diabetes, deafness and unusual neurological symptoms. We herein report an unusual presentation of MIDD in a 39 year female who presented with gestational diabetes during her 5th pregnancy. On high clinical suspicion genetic testing was done showing mutation in mitochondrial DNA (3243 A > G). She was treated with insulin during pregnancy and given Metformin and Gliclazide post-natal. After establishing final diagnosis of MIDD, her Metformin was stopped due to risk of lactic acidosis. She was continued on other oral hypoglycaemic agents with dietary changes and offered genetic counselling. MIDD is associated with co-morbidities and unique management issues. There is no definite evidence of efficacy for any specific therapy. Oral hypoglycemics can be helpful initially but patients may require insulin therapy within 2 years after diagnosis. The effectiveness of other treatment options described in literature including Co enzyme Q and thiamine requires further study.
Keywords: maternally inherited diabetes and deafness, mitochondrial DNA, mutation, gestational diabetes.

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AEP1039

Impact of obesity on types of myocardial infarction

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Introduction
Obesity is an independent risk factor of coronary artery disease, and it has also been shown to be associated with increased survival in some instances such as myocardial infarction – dubbed the 'Obesity Paradox'. However, there is a paucity of studies identifying the type of myocardial infarction – non-ST-segment elevation MI (NSTEMI) or ST-segment MI (STEMI) – that may be differentially prevalant according to BMI (body mass index) class. Indeed, STEMI has been shown to have better long-term mortality compared to NSTEMI, and may contribute towards improved survival among the obese population.
Hypothesis
We hypothesised whether STEMI or NSTEMI is greater in obese patients and if increasing BMI correlates with increased likelihood of STEMI.
Methods
We retrospectively analysed 1649 patients from a larger cohort of patients from the local cardiac surgery database collected from 2010 to 2019. BMI (weight [kg]/height^2 [m^2]) was calculated for all patients which were then assigned into groups (normal [BMI 18.5–24.9], overweight [BMI 25–29.9], and obese [BMI ≥ 30]). Baseline characteristics were assessed, including a history of cardiovascular risk factors and biochemistry. The prevalence of the MI type (as either STEMI or NSTEMI) was calculated for each BMI group. The MI type was correlated against BMI groups adjusted for cardiovascular risk factors and biochemical parameters associated with the metabolic syndrome including low-density lipoprotein (LDL), triglycerides, and fasting blood glucose.
Results
NSTEMI was more prevalent across all BMI groups compared to STEMI. NSTEMI was more prevalent (STEMI less prevalent) in both the obese and overweight groups when compared to the normal BMI group (82.4% vs 71.1%, $P = 0.001$, and 79.8% vs 71.1%, $P = 0.008$ respectively). There was no significant difference in the prevalence of NSTEMI or STEMI between obese and overweight BMI classes (82.4% vs 79.8%, $P = 0.34$). Further analysis of the type of MI with ordinal logistic regression revealed a reduced likelihood of STEMI with increasing BMI class (OR: 0.57 ± 0.16, 95% confidence interval 0.33–0.97, $P = 0.042$) and is statistically significant when adjusted for above co-variates.
Conclusion
This studied showed that NSTEMI was more prevalent relative to STEMI amongst high BMI patients. Increasing BMI was associated with reduced likelihood of STEMI. Although these findings are in contrast with our hypothesis, it highlights the impact of obesity on MI presentations. This may have clinical and/or practical implications on the management of MI in the obese population and further studies are warranted in this context.

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AEP1040

Differences in health-related quality of life between type 1 and type 2 diabetic patients in Austria

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Background and aim
Improving the quality of life is one of the main goals of treating diabetic patients in addition to manage glycaemic control and diabetes complications. The study aim was to assess and compare the quality of life among Austrian patients with type 1 and type 2 diabetes mellitus using the German version of the World Health Organization Quality of Life-BREF instrument (WHOQOL-BREF).
Methods and Materials
This was an observational study that included $n = 208$ patientsfrom the Diabetes center in Melk General Hospital, Lower Austria region. Of those, $n = 170$ were diagnosed with type 2 and $n = 38$ with type 1 diabetes. Quality of life was assessed using the German version of the WHOQOL-BREF questionnaire over one year from 2018 to 2019. Consisting of questions about psychological, physical, social, and environmental topics, the WHOQOL-BREF questionnaire covers four main domains. The response to each item in the questionnaire scored from 1 to 5 (ranged from strongly disagree

to agree strongly) on the Likert scale. The raw scores in each domain were transformed into a 0 to 100 score according to the WHOQOL-BREF manual. For statistical analysis, we used R–project for statistical computing, and the Mann–Whitney U test (Wilcoxon rank-sum test) was used to compare Quality of life according to the type of diabetes.
Results
The mean HbA1c values for type 1 and type 2 patients were 61.5 mmol/mol (7.8%) and 55.5 mmol/mol (7.2%) (n.s.), respectively. 61% of all patients were male. The WHOQOL-BREF scores among both type 1 and type 2 diabetes patients were relatively high, which reflects good quality of life. Scores of the physical domain were higher in type 2 diabetes patients than in type 1 diabetes patients (64.5±20.1 vs 50.5±5.2, $P<0.001$). Similarly, scores of the environmental domain were higher in type 2 than in type1 (84.4±11.2 vs 80±3.3, P 0.04). The scores of the psychological and social domains did not differ between the two groups (71.3±18.1 vs 72.2±16.7, $P=0.88$, and 70.1±20.1 vs 71.0±19.6, $P=0.19$, respectively.
Conclusion
This study showed that type 2 diabetic patients significantly scored higher in physical and environmental domains compared to type1 diabetic patients. Further research is needed to examine this issue in detail and also the causes that may influence the quality of life in each type of diabetes.

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AEP1041

Assessment of association between VDR variants and type 2 diabetes in an elderly greek population

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Background
Vitamin D receptor (VDR) in the presence of active calcitriol (1.25-dihydroxy vitamin D) acts as a transcription factor that modulates the gene expression oftransport proteins, which are involved in calcium metabolism. Accumulating evidence suggest apotential implication of vitamin D deficiency in the pathogenesis of diabetes mellitus. We aimed toassess whether variants in the *VDR* gene contribute to risk of Type 2 Diabetes Mellitus (T2DM).
Methods
Twenty-five polymorphisms within *VDR* gene were genotyped in 716 patients with T2DM (group A) and 569 controls (group B) of Greek origin, 393 of which withoutprediabetes (group C). Group B consisted of elderly above 65 years of age with documentedabsence of T2DM (HbA1c<6.5% and fasting plasma glucose (FPG)<126 mg/dl). Participants from group B with HbA1c levels<5.7% and FPG<100 mg/dl were selected to form a control subgroup (group C). DNA samples were collected after informed consent was obtained and they were analyzed on Illumina Human PsychArray. After quality control, polymorphisms in *VDR* gene were selectedand allele frequencies between groups were compared. Permutation test analysiswas implemented to determine statistical significance. P-values <0.05 were regarded as significant.
Results
Two analyses were undertaken. The first, between group A and group B revealed nosignificant association between T2DM and *VDR* variants with either recessive or dominant model. The second, between group A and group C showed that rs7967152 ($P=0.0276$, OR=1.234)associated significantly with T2DM. Recessive model analysis revealed that AA genotype ofrs7967152 ($P=0.027$, OR=1.543) and TTgenotype of rs12301817 associated significantly with disease ($P=0.037$, OR=0.494).
Conclusion
Our results are indicative of the complexity of T2DM geneticsusceptibility and partly reflect the controversy in the literature regarding the role of vitamin D metabolism in T2DM pathogenesis. Further studies are required to replicate our findings and clarify any complexunderlying mechanisms of action that could contribute to T2DM development.

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AEP1042

A case of intentional overdose of insulin glargine and lispro treated with hydrocortisone

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Introduction
Patients with diabetes have nearly twice the risk of depression compared to general population. Prolonged hypoglycemia can occur with insulin overdose and treatment involves correction of hypoglycemia with oral or intravenous glucose supplementation, with glucagon or octreotide in some cases. Glucocorticoids are not routinely administered but can be used as an adjunct in severe cases. We present a case of intentional insulin overdose in a young diabetic patient with hypoglycemia who responded to additive intravenous hydrocortisone after showing minimal response to repeated administrations of dextrose.
Case description
A 29 year-old female with history of secondary diabetes from chronic pancreatitis with CFTR mutation and previous autologous islet transplantation presented to the emergency department with recurrent episodes of hypoglycemia that persisted despite ingesting high carbohydrate foods. She had a history of self-harm attempts. The patient was using an insulin pump in manual-mode and continuous glucose monitor. She reported that her insulin pump malfunctioned and took reduced dose of 12 units of insulin glargine from a 24-hour basal of 16.8 units the night prior to admission. Serum glucose on presentation was 57 mg/dl requiring 10% dextrose boluses every hour in addition to a dextrose infusion. Hypoglycemia persisted for over 12 hours since admission with lowest point-of-care glucose 19 mg/dl. She eventually admitted to taking 1 full pen of insulin lispro and 1 full pen of insulin glargine; 300+300 units=600 units. For resistant hypoglycemia, a trial of IV hydrocortisone 100 mg followed by 50 mg 8 hours later resulted in subsequent improvement in glucose levels greater than 90 mg/dl. The patient later admitted that she never modified her pump settings and there was no malfunction.
Discussion/Conclusion
Our patient responded well to addition of hydrocortisone with improvement in hypoglycemia within hours after administration. Treatment with glucocorticoids has shown to counteract the resistant hypoglycemia due to insulin overdose in previous case reports. This case highlights a challenge of initial diagnosis due to patient limited disclosure and to consider high risk factors like previous suicide attempts, anxiety and depression in evaluation of hypoglycemia. Careful management of symptoms related to depression and developing a safety plan is integral to complete patient care. In conclusion, our case emphasizes the importance to recognize high risk factors for self-harm in diabetic patients and consideration for early intervention with glucocorticoids for persistent hypoglycemia if insulin overdose is suspected.

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AEP1043

Trabecular bone score and insulin resistance in type 2 diabetes mellitus

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Introduction
Trabecular Bone Score (TBS) is a new non-invasive method to evaluate trabecular bone quality at the lumbar spine. The literature has contradictory results concerning the influence of insulin resistance and adipose tissue on bone, for this reason it is of interest to evaluate factors that determine bone health and risk of fracture in patients with T2DM.
Objective
To analyze the relationship between insulin resistance and adipose tissue with bone microarchitecture in patients with T2DM.

Materials and methods
Cross-sectional observational study. We included 137 T2DM patients,mean age 65.2±7.5 years (58% male, 91% overweight/obese) and 300 non-diabetic controls. Demographic, anthropometric, clinical and biochemical variables were studied. To estimate whole-body fat percentage, we used a simple anthropometric linear equation named as the relative fat mass (RFM): 64 – (20 × height/waist circumference)+(12 × sex); sex=0 for men and 1 for women. We determined bone mineral density in the lumbar spine, femoral neck and total hip by dual X-ray absorptiometry (DXA, Hologic QDR 4500), and TBS values using TBS iNsight Software, Med –Imaps, Pessac France). Statistical analysis was performed using the SPSS program (SPSS, inc, v 25.0)
Results
Patients with T2DM show significantly lower TBS values (1.08+ 0.18 vs 1.28+0.15 $P<0.000$) despite of significantly higher lumbar BMD (LS-BMD) (1.05+0.20 vs 0.90+0.52 $P<0.001$) compared to those without diabetes. TBS values were negatively correlated with body mass index (BMI) ($P<0.000$),waist circumference ($P<0.000$) and HOMA-2IR index ($P=0.004$). However, no correlation was found between these parameters with LS-BMD. RFM was negatively correlated with both LS-BMD ($P<0.000$) and TBS ($P=0.005$) in patients with T2DM. In the multivariate analysis the association between TBS and insulin resistance parameters was maintained after adjusting for age and RFM.
Conclusions
This study shows that BMI, RFM, waist circumference, and insulin resistance are associated with lower TBS values in patients with T2DM. Our study suggests that central adiposity and its metabolic consequences negatively affect bone quality in these patients despite normal or increased bone density.

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AEP1044

Incidence of large-for-gestational age newborns is still elevated in women with type 1 diabetes in good glycaemic control

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Introduction
Glycemic control has a major effect on fetal growth in women with type 1 diabetes mellitus (DM1), worse control leading to increased growth (large for gestational age (LGA) or very large for gestational age (VLGA) fetus). Current guidelines promote strict control (HbA1c≤48 mmol/mol) before and during pregnancy. Continuous glucose monitoring (CGM) has been instrumental in achieving this goal. We performed a retrospective chart review of pregnancy outcomes in DM1 to assess Outcome and CGM-data in well-controlled women with DM1.
Methods
Forty-eight pregnancies in 25 women were identified between 2016–2019; 19 women with a singleton pregnancy met the inclusion criterion of HbA1c≤48 mmol/mol in first and third trimester. In 8 women there were insufficient CGM-data: final CGM-study group of 11 women. LGA was defined as fetal weight>90th and VLGA>97.7th percentile. CGM-data were studied during 4 periods: 4–8 weeks gestation, 18–22 weeks, 30–34 weeks and last 8 days before delivery. Target range 3.5–7.8 mmol/l. Time in range (TIR), time below range (TBR) and time above range (TAR) were calculated.
Results
In the group of 19 women with adequate control, LGA (both LGA and VLGA) in 36.8%; simple LGA 15.7%, VLGA 21.1%.In none of the pregnancies congenital malformations were seen. Women with a VLGA child were significantly older ($P<0.03$), had higher BMI ($P<0.02$) and longer duration of DM1 ($P<0.02$). In women with normal growth fetus, LGA or VLGA, TIR was 64.1%, 63.6% and 58.5%; TAR: 24.4, 34.4 and 39.6%; TBR: 4.0, 2.2 and 2.1. Classic multivariate logistic regression analysis did not show statistical significance.
Conclusion
Our data show that current implementation of advanced technology did not have a great effect on fetal growth parameters. Mean TIR was below the recommended level in the newest guideline published in Diabetes Care in June 2019. Apparently, adaptation of endocrine care and counselling strategies are needed for improvement in outcome with technology.

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AEP1045

Variation in relative abundance of gut bacteria correlates with lipid profiles in adults

Abstract unavailable

AEP1046

The association of glomerular filtration rate with coronary artery disease in type 2 diabetic patients

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Background and aim
Chronic Kidney Disease and Diabetes Mellitus can influenceCoronary Artery Disease (CAD) independently. The aim of this study was to evaluate the association of Glomerular Filtration Rate (GFR) and Coronary Artery Disease in type 2 diabetic patients. (T2DM)
Methods
This cross sectional study evaluated 362 T2DM patients with clinical presentation of CAD whose documents were registered in angiography center during 18 months. GFR was measured by MDRD method and divided into 5 subgroups: GFR<15, 15≤GFR<30, 30≤GFR<60, 60≤GFR<90 and GFR≥90. Then the association of 5 subgroups of GFR with coronary angioplasty in T2DM patients was evaluated. The association between age, sex, hypertension, and dyslipidemia with 5 subgroups of GFR was also studied.
Results
Among 3624 T2DM patients, 36% had GFR<60 (ml/min/1.73 m^2).The highest frequency percentage of coronary angioplasty (53%) was observed in the GFR stage 3 (30–60) ml/min/1.73 m^2. A significant inverse association was observed between the GFR of T2DM patients and the frequency percentage of coronary angioplasty. (P-value<0.001).There was also a significant association between GFR<60 and history of hypertension and dyslipidemia. (P-value<0.001). Using regression analysis, it was shown that GFR can be an independent factor to predict coronary artery disease. (P value=0.02, $\beta=1.003$).
Conclusion
A reduced GFR in patients with diabetes increases CAD, independently of other risk factors.

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AEP1047

Prediction of weight loss response to liraglutide

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Background
Obesity is a significant risk factor for type 2 diabetes mellitus (T2D), hypertension and ischemic heart disease development. Moreover, in patients with already diagnosed T2D, obesity puts a crimp in achievement of glycemic target. Thus, body weight reduction is important both to prevent T2D and to treat it successfully. However lifestyle habits, diet and physical activity are the key factors of T2D prevention and treatment, eating disorders and disturbed appetite control decrease compliance to these efforts. Liraglutide is successfully used for such cases leading to significant weight reduction, followed by improvement of hypertension and dyslipidemia. However its efficacy varies a lot, and its cost negatively influence treatment compliance. The aim of this study was to reveal patients' parameters likely leading to higher treatment efficacy.
Methods
We tested 41 patient with obesity with mean (± S.D.) BMI of 39.63±7.59 kg/m^2: 27 injecting liraglutide up to 1.8 mg/day and 14–3.0 mg/day for 6

months. We gathered demographic and anthropometric data, parameters of glycemic control, insulin, C-peptide GLP-1, GIP and leptin blood concentration, results of Dutch Eating Behavior Questionnaire and answers to questions about hunger with the use of visual analogous scale at fasting state. We considered a therapy response as ≥7% bodyweight reduction after 6 months of treatment. We used Mann-Whitney U-test to compare responders and non-responders in terms of gathered parameters and linear regression model (LRM) to reveal parameters possibly associated with better weight-reduction response.
Results
We confirmed a dose-dependent liraglutide efficacy in routine clinical practice (more responders in 3.0 mg/day group, $P=0.007$). Responders without T2D had a 1.7-fold lower leptin concentration as compared to non-responders ($P=0.018$). LRM was not statistically significant due to a small sample ($P=0.098$), however regression coefficient was –0.50. In responders without T2D GLP-1 level before therapy initiation positively correlated with body weight reduction ($B=0.84$; $r=0.60$; $P=0.031$). Questions about hunger ('how gorged are you' and 'how much could you eat now') showed $r=0.51$ and –0.46, respectively, however were not statistically significant ($P=0.064$ and 0.097, respectively). Liraglutide was ineffective in BMI > 45 kg/m^2. Other factors were not significant for our data.
Conclusion
Lower leptin and higher GLP-1 concentrations might predict better weight-loss response to liraglutide. Questions about hunger at fasting state might be strong response predictors (need for evaluation at bigger sample). Liraglutide is probably more effective in BMI 30–45 kg/m^2.

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AEP1048

Diabetes and COVID-19

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Background
Although obesity and has been associated with COVID-19 mortality, the absolute and relative risks for Type 2 diabetes (DM2) is unknown. The aim of this study was to analyse metabolic characteristics of patients infected by COVID-19 hospitalised and evaluate whether DM2 have an impact in this group of patients.
Methods
We retrospectively analysed data of COVID-19 patients hospitalized to a large academic hospital system in Zaragoza between March 6st and April 02th, 2020. Data included demographics, comorbidities and biochemical parameters. The time-dependent probability of death was evaluated using the Kaplan-Meier method. Univariable and multivariable logistic regression models were performed. P value < 0.05 was considered significant.
Results
The study included 149 patients (87 men) with a mean age of 67.91 years (s.d. 17.03). Hypertension (50.3 %), dyslipidemia (23.5%) and diabetes (20.8%) were the most prevalent comorbidities. By multivariable regression analysis, both Charlson comorbidity index (CCI) (OR 1.627, CI 95% [1.183–2.321] $P=0.01$)and a neutrophil to lymphocytes ratio (NLR) > 10 (OR 4.249, CI 95% [1.419–12.724] $P=0.010$)were associated with a higher risk of COVID-19 mortality. In univariate proportional analysis DM2 (OR 4, CI 95% [1.708–9.367] $P=0.01$), was associated with mortality, but it was not significant in the multivariable analysis.
Conclusion
Our study demonstrates that hospitalized patients with DM2 are more likely to die from COVID-19. CCI and NLR were both good predictors of mortality in this population.

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AEP1049

Diabetic emergencies during COVID-19 –A multi-centre experience

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Introduction
Diabetes mellitus is as a major contributor to disease severity and mortality in patients with Covid-19 infection, as the estimated increase in risk of death in hospitalised patients is 3.5-times (for T1DM) and 2.03-times (for T2DM). This retrospective analysis recruited 35 patients from three London hospitals who presented with diabetic emergencies i.e. diabetic ketoacidosis (DKA), Hyperglycaemic hyperosmolar state(HHS), presence of ketoneamia (beta-hydroxybutyrate >0.6 mmol/l) as well as with positive SARS-CoV-2 PCRduring March 2020.
Results
Median age was 60 years (male 67.5%). 11 (31.4%) of patients had DKA, 13 (37.1%) patients had mixed DKA and HHS picture, 9 (25.7%) presented with hyperglycaemic ketosis and 2 (5.8%) patients had HHS. 17(48.6%) were of African origin and 6 (17.1%) mixed race.80% had T2DM and 5.7% had new diagnosis of diabetes. Across all cases the degree of ketoneamia was negatively correlated with pH (P-value = 0.035), HCO3 (P-value < 0.001) and base excess (P-value = 0.001). Time to ketone resolution was positively associated with fluid volume required (P-value = 0.047) and negatively correlated with pH (P-value = 0.025), HCO3 (P-value = 0.015) and base excess (P-value = 0.007). Median time taken to ketone resolutionfor all patients was 24 hr (IQR 14.6–36), and 35hr (IQR 24–60) for DKA. Median time to ICU admission was 3.00 ± 1.23 days, median length of stay for discharged patients was 18.0 ± 3.98 days. 13 patients were still inpatients at the time of study, 5.7% ($n=2/35$) of patient'snon-insulin treated previously, had died (DKA $n=1$; mixed DKA/HHS $n=1$).
Conclusion
This study shows overrepresentation of T2DM amongst patients admitted with DKA in the context of Covid-19 infection. Our patients, mainly of African/Afro-Caribbean background, had protracted ketoneamia and ketoacidosis with prolonged time to resolution.
These results indicate a possible effect of the ethnic background on the clinical outcome in patients admitted with diabetes emergencies in the context of Covid-19 infection. Large scale observational studies are needed to understand the insulopenic effects of COVID-19.

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AEP1050

The impact of strict COVID-19 lockdown in spain on glycemic profiles in patients with type 1 Diabetes prone to hypoglycemia using standalone continuous glucose monitoring

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Aims
Spain has been one of the worst affected countries by the COVID-19 pandemic. A very strict lockdown at home was imposed with a tough restriction of mobility. We aimed to evaluate the impact of this exceptional scenario on glucose profile of patients with type 1 diabetes (T1D) prone to hypoglycemia using standalone continuous glucose monitoring.
Methods
Patients with T1D prone to hypoglycemia using multiple daily injections and either a Dexcom G5 or a Free Style Libre CGM systems for at least 6 months under the funding of National Health Service were included in an observational, retrospective study. Data were collected in two periods: pre-lockdown (PL), February 23rd–March 7th and within lockdown (WL), April 1st–14th 2020. The primary outcome was the difference in the proportion of time in target glucose range of 70–180 mg/dl (TIR). Additional glucometric data were also analysed.
Results
92 patients were included: 40 women, age 42.8 ± 3.9 years, disease duration of 23.1 ± 12.6 years. Seventeen patients used Dexcom G5 and 75 Free Style Libre. TIR 70–180 mg/dl (59.3 ± 16.2 vs 62.6 ± 15.2%), time >180 (34.4 ± 18.0 vs 30.7 ± 16.9%), >250 (11.1 ± 10.6 vs 9.2 ± 9.7%) and Glucose Management Indicator (7.2 ± 0.8 vs 7.0 ± 0.8) significantly improved (PL vs WL, respectively, $P<0.05$). Time in hypoglycemia remained unchanged.
Conclusions
Lockdown conditions imposed by the COVID-19 pandemic may be managed successfully in terms of glycemic control by population with DT1 prone to hypoglycemia using CGM. The strict daily routine at home could probably explain the improvement in the time in glycemic target without increasing the time in hypoglycemia.

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AEP1051

Clinical characteristics and outcomes of COVID-19 hospitalized patients with diabetes in the United Kingdom: A retrospective single centre study

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Aim
To describe the clinical characteristics and outcomes of hospitalized COVID-19 patients with diabetes.
Methods
A retrospective cross-sectional study was conducted among patients admitted to the William. Harvey Hospital in England between March 10th and May10th, 2020 with a laboratory confirmed severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), known as COVID19. Variation in characteristics, length of stay in hospital, diabetes status, duration of diabetes, control of diabetes, comorbidities and outcomes were examined.
Results
There were 232 COVID-19 presentations. Mean (standard deviation (S.D.), range) age was 70.5 (± 15.7, 30–101) years, 62.5% were male, and 37.5% were having diabetes. There were 43.4% males and 27.6 females, $P=0.016$, with diabetes admitted to our hospital due to COVID-19. Patients with diabetes were more likely to have longer length of stay (LOS) in hospital, 14.4 (S.D. ± 9.6) days, compared to the patients without diabetes, 9.8 (S.D. ± 17.1) days, $P<0.0001$. Patients with diabetic ketoacidosis (DKA) were more likely to survive (87.1%) compared to patients without DKA (50.6%), $P=0.046$.
Conclusion
Males were more likely to be admitted to hospital with COVID-19 illness than females. Hospitalized COVID-19 patients with diabetes had a longer LOS in hospital than patients without diabetes. Older age COVID-19 patients with diabetes and patients without DKA were less likely to survive compared to younger patients and patients with DKA, respectively. Further studies with large sample size are needed.
Keywords: COVID-19, diabetes, diabetic ketoacidosis, length of stay.
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AEP1052

Characteristics and outcomes in COVID –19 with Type 2 diabetes as compared with patients without diabetes – Retrospective single center cohort study

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Introduction
COVID 19 is now a global pandemic. Diabetes is postulated to be a risk factor for mortality due to COVID –19
Methods
We retrospectively evaluated the inpatient medical record data, of patients admitted over last two months in a public hospital in Central India to compare the attributes of mortality in patients without T2DM and with T2DM including their glycemic clinical characteristics. Unpaired t – test and Fisher's exact test was utilised for statistical analysis
Results
We analysed a total of 350 COVID –19 patients (204 males, 146 female). The mean age of cohort was 34 years (± S.D. 18, 95% CI 32 to 36). There were 25 (7.14 %) patients with T2DM (13 males) and 325 (92.8 %) patients did not have T2DM (noT2DM). Mean age in T2DM was 54 years (± S.D. 12, 95% CI 49 to 59, min 23, max 73) and in noT2DM was 32 years (± S.D. 18, 95% CI 30 to 34, min 0.1, max 84); $P<0.0001$. Of seven patients who expired, two had T2DM (both males), two had both hypertension with TDM and one had only hypertension. Overall mortality was 2% (7/350), 8 % (2/25) was reported in T2DM which was higher than in the noT2DM 1.5% (5/325). The relative risk of mortality in T2DM as compared to noT2DM was 0.93 (95% CI 0.76 to 0.99), $P=0.082$ (NS). The mean days of illness to mortality was 4.5 days in T2DM as compared to 5.5 days in the NoT2DM group. Among, the two T2DM patients who expired, one presented with severe acute respiratory illness and other with history of contact. Mean Random Blood Sugar (RBS) at the time of admission in T2DM was 183 mg/dl (± S.D. 71, 95% CI 154 to 212, min 78, max 296). The mean RBS in patients who expired was 255 mg/dl, with 72 mg/dl higher than the overall T2DM group. One T2DM who expired had ketoacidosis.
Conclusions
Our results are in line with the emerging global data that postulate that the mortality rates would be much lower than what was documented in the earlier studies. However, patients with T2DM and elderly are at higher risk for death. It is imperative in T2DM to achieve good glycemic control to mitigate the complication of mortality due to COVID 19
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AEP1053

Case of steroid diabetes in a female with the hemophagocytic syndrome and panniculitis of Weber-Kristen

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39-year old female reported usage of methylprednisolone (20–80 mg daily) for three months since the last decade of January 2020. She received methylprednisolone for controlling of panniculitis of Weber-Kristen (diagnosis was proved twice histologically in Ukraine and Austria. Before starting steroid therapy, there was no glucose impairment in her history. The patient has different complaints, including fatigue, increased body temperature, hypersensitivity of the skin, vomiting, wound on her back (after biopsy for four months), polyserositis, menometrorrhagia. The patient was hospitalized to the private medical center 'Universal Clinic 'Oberig' in May 2020 and stayed there for a week. During hospitalization condition of the patient was critical due to general inflammatory, hemorrhagic, pancytopenia, severe liver disorders, with some trend to worsening despite the therapy. The ANA-screen test was negative. Sepsis was not proved (in blood, there was no bacterial growth). She did not have any signs of infectious endocarditis on echocardiography. Results of myelography reported the absence of acute leucosis, but there were signs of aplasia and dysmonopoesis. Trepan biopsy was not performed in Kyiv as the patient disagreed. Liver tests were extremely high (data on the presence of viral hepatitis was not proved). Severe pancytopenia (leucopenia was 0.44 G/l, thrombocytopenia was 58 G/l, hemoglobin was 74–95 g/l), and coagulopathy (starting from hypocoagulation to the absence of coagulation) was observed and corrected all the time. Results of PET CT in February 2020 did not report the data of any solid tumor, except some signs of panniculitis. The usage of methylprednisolone had a temporary effect. Glycated hemoglobin was slightly increased, and during glucose monitoring, there was almost compensated diabetes (sometimes we used insulin for correcting hyperglycemia). The patient was discharged from the hospital according to her wish as she planned to be hospitalized in Austria. In Austria, she was hospitalized to the intensive care unit in some hospital and then to hematological as there were signs of hemophagocytic syndrome. Unfortunately, the patient died due to progression of the disease (hemorrhagic stroke happened). This case is rare, and it describes comorbidity of panniculitis of Weber-Kristen, hemophagocytic syndrome, and steroid diabetes.
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AEP1054

A pilot trial for silymarin in prediabetic patients with preclinical liver disease: Focus on insulin resistance

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Introduction
Silymarin is a standardized extract of the milk thistle (Sylibum marianum) seeds, containing a mixture of flavonolignans: silybinin, isosilybinin, silycristin, silydianin, and others. It is used in the treatment of toxic liver

damage and as adjunctive therapy in chronic hepatitis and cirrhosis. Recent studies have shown a potential benefit in the treatment of diabetes mellitus and non-alcoholic fatty liver disease. We undertook to study the effect of silymarin on insulin sensitivity in prediabetic patients with preclinical liver disease.
Methods
For this open, uncontrolled trial, patients 18–75 years old of both sexes with prediabetes and moderately elevated transaminases or GGT (<3 × ULN) were assigned for treatment twice a day for 3 months with a capsule containing silymarin (196 mg) plus Agrimonia eupatoria extract (166 mg) plus Lamium album extract (166 mg). The main endpoint was the change in the HOMA-2 index of insulin resistance (https://dtu.ox.ac.uk/homacalculator). Secondary endpoints: effects on fasting glucose, insulin, HbA_{1C}, and the change of status from prediabetes to normoglycemia or diabetes mellitus. Tertiary endpoints: changes in AST, ALT and GGT. Additional endpoints: changes in BMI, lipid profile, blood pressure and heart rate. Security endpoints: Reported adverse effects and compliance (by questionnaire).
Results
11 patients were recruited (64% women, age 49.3±12.3 years, BMI 32.2±6.3 kg/m^2). The HOMA-2 index was significantly reduced from 3.49±0.58 to 2.96±0.49 (P=0.043, paired t-test). Fasting insulin, but not fasting glucose or HbA_{1C}, was also significantly reduced. 2 patients changed status to normoglycemia but none progressed to diabetes mellitus. AST, ALT and GGT were significantly reduced. BMI, lipid profile, blood pressure and heart rate did not change significantly, but there was a trend for reduced triglycerides and increased HDL-cholesterol. The mean reported compliance was 87% and no serious side effects were reported; no patient withdrew from the study.
Conclusions
The combined extracts of Silybum marianum, Agrimonia eupatoria and Lamium album were well tolerated and able to ameliorate the insulin resistance of prediabetic patients with preclinical liver damage, mainly by decreasing their fasting insulin. The liver enzyme profile was also improved. This combination could be expected to reduce the long term risk of progression to type 2 diabetes in these patients. The limitations of this pilot trial are obvious, but a full-scale trial seems warranted.

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AEP1055

The effects of selective activation of kisspeptin neurons in hypothalamic arcuate nucleus on energy metabolism in mice

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Objectives
This study aims to determine which metabolic tissue is involved in the process of kisspeptin neurons regulate energy metabolism so that it may provide a novel therapy for metabolic related diseases such as obesity.
Methods
Kiss1-CreGFP mice were used in this study. And we selectively activated kisspeptin neurons by using Designer-receptors-exclusively-activated-by-designer-drugs (DREADDs) technology. Mice were bilaterally injected with the Cre-dependent adeno-associated viral (AAV) vector encoding human M3-muscarinic receptor (hM3Dq) fused with red fluorescent protein in ARC. And peripheral administration with clozapine N-oxide (CNO) leads to CNO-dependent activation of kisspeptin neurons in ARC (kiss1ARC), then, we studied metabolic phenotype of mice.
Results
Neuronal activation of kisspeptin neurons with DREADDs decreases body weight, daily average food intake, and increases energy expenditure by altering brown adipose tissue (BAT) thermogenic process and browning of white adipose tissue (WAT), which is depend on different energy states only in female mice.
Conclusions
Our results previously demonstrated that kisspeptin neurons play crucial role in controlling energy metabolism, which is sexually dimorphic.

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AEP1056

Levels of lymphocytes subpopulations in peripheral blood among patients with diabetes mellitus type 2

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Aim of the study was to investigate the lymphocytes (lymph) subpopulations as a part of immune response in peripheral blood among the patients with Diabetes mellitus type 2 (DMT2).
Patients and methods
A prospective, cross-sectional, comparative, 'case-control' study was conducted among 70 patients with DMT2. The levels of lymph subtypes[general nonspecific T-lymph (CD3+); T-helper lymph (CD4+); T-cytotoxic lymph (CD8+), natural killers [NK cells (CD3\ CD16+/CD56)] and B-lymph (CD19+)] in blood was measured and compared by flow-cytometric analisys (FAC Sort, BD).Results were compared to those of 22 patients with Diabetes mellitus type 1 (DMT1) and 21 healthy persons. The data was processed using the statistics software.
Results
No significant differences between arterial blood pressure, HвA1c levels and lipid profile among the patients with DMT1 and DMT2. No differences in the total leukocyte count between diabetic persons (DMT1–6.91±1.32.10^9/l; DMT2–7.28±1.85.10^9/l; controls-6.89±1.07.10^9/l). The results from flow-cytometric investigation showsignificantly higher absolute number of T-all lymph (CD3+), Th lymph (CD4+) and all NK (CD3\ CD16+/CD56), as well as a lower absolute number of Ts (CD8+) and B (CD19+) lymph among the diabetic patients compared to healthy subjects. The Th/Ts ratio in patients with DMT1 (2.02±0.44) and DMT2 (2.36±0.37) is also significantly higher compared to ratio of controls (1.02±0.06). No significant differences in the lymph subpopulations between the two groups with DM.
Conclusions
Changes of lymph types in peripheral blood in diabetic patients demonstrate immune activation and dysregulation among the two types of diabetes.
Keywords: type 1 diabetes mellitus, type 2 diabetes mellitus, flow- cytometry, lymphocytes.

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AEP1057

Role of insulin aspart fiasp in patients with diabetes mellitus

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Introduction
Postprandial glycemic control is complex as well as insufficient. Its impact on global metabolic control (HbA1c) is controversial with various works that support its influence in terms of glycemic variability and genesis of micro and/or macrovascular complications. Fiasp due to its special formulation allows a more effective control of postprandial glycemia being an interesting alternative to the rapid-acting insulin analogavailable.
Objective
To assess the impact of FIASP insulin on global metabolic control (HbA1c) and patient adherence to this new formulation.
Materials and methods
Prospective study of 82 patients with DM followed up in two hospitals in Granada whose initial 'fast' insulin was replaced by FIASP. Two groups are theorized: 1. HbA1c>8.5% (greater influence of poor control of basal glycemia) and 2. HbA1c<8.5% (greater influence of poor postprandial control). The statistical study was carried out with the SPSS15 program.
Results
82 patients (52.4% women) with a mean age of 41.54±16.9 years. Evolution time of DM of 15.9±9.40 years. 78% of DM1 patients, all in bolus basal regimen. Average basal insulin dose of 30.47±14.89 IU (0.42 IU/kg). Basal 'fast' insulin: 8% aspart, 16.9% glulisine, 20.9% lispro and 1.2% human rapid. Baseline HbA1c and blood glucose values of 8.65±1.49% and 148.23±71.34 mg/dl respectively. After a mean follow-up of 7.9±3.5 months (67 patients with data available at follow-up), HbA1c and baseline blood glucose values were 8.20±1.22% (P<0.05) and 132, 67±62.71 mg/dl (NS) respectively. A greater decrease in HbA1c was observed in those patients with baseline HbA1c>8.5 (P<0.05). During the follow-up, 26.8% of the patients needed to decrease the doses with respect to the rapid insulin

they used previously and 12.2% decided to stop Fiasp and return to their initial rapid insulin.
Conclusions
Fiasp improved metabolic control in a large group of patients with DM, especially in the group with baseline HbA1c > 8.5. Adequate information to the patient about the characteristics of said insulin is necessary in order to increase adherence and achieve the potential benefits expected with this formulation.

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AEP1058

Changes in metabolic control and body composition with Semaglutide sc in patients with type 2 diabetes mellitus

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Objectives
aGLP1 have been positioned as an effective and safe treatment in patients with Type 2 Diabetes Mellitus (DM2). The objective was to evaluate the changes metabolic and body composition at 6 months after initiation with Semaglutide weekly subcutaneous added to its basic treatment in patients with DM2.
Material and methods
Prospective observational study. Treatment was started in 42 patients with DM2, with weekly subcutaneous Semaglutide with a 6-month follow-up. We studied clinical, biochemical, anthropometric and body composition changes. In addition, treatment adherence, side effectsand changes in dietary habit were evaluated. The body composition study was performed with Tanita TBF-300 impedancemeter. Statistical analysis was performed through the SPSS program (SPSS, inc, v 15.0).
Results
42 patients with DM2 were recruited. Average age was 61 ± 9.7 years, 54.8% males. Baseline data: A1c 8.75 ± 1.8%, baseline blood glucose 176.55 ± 62.7 mg/dl, BMI 35.98 ± 7 kg/m^2, SBP 138.7 ± 16.8 mmHg. In basal impedanciometry, the average fat mass (%), lean mass (kg) and total water (kg) was 38.1 ± 7.94%, 60.8 ± 9.9 kg and l 44.5 ± 7.2 kg respectively. 40.4% had established CVD, preferably MI. Base treatment: 64.3% metformin, 35.7% iSGLT2, insulin: 50% basal insulin analog and 11.9% rapid insulin analogues and 71.4% statins. After 6 months of treatment there were statistically significant reductions in A1C (–1.85 ± 2.09%), baseline blood glucose (–47.9 ± 74.54 mg/dl), weight (–4.92 ± 4.2 kg), BMI (–1.88 ± 1.66 kg/m^2), SBP (–12.1 ± 15.5 mmHg), LDL (–17 ± 42.5 mg/dl), TG (–44.1 ± 118.37 mg/dl) and fat mass (–2.66 ± 4.37 kg). The presence of iSGLT2 in the treatment did not influence the results. Treatment adherence was 55%. 71.4% reported a greater feeling of postprandial fullness. We did not detect serious adverse effects. 50% of patients made changes in their habits diet after the introduction of semaglutide.
Conclusions
In our experience, Semaglutide treatment is very effective and sure producing very beneficial changes at metabolic level, in body composition, blood pressure, lipid profile and even dietary patterns in patients with Type 2 diabetes mellitus 6 months after the start of treatment. It is necessary collaboration strategies between patients, educators, and physicians to improve adherence to treatment.

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AEP1059

Coronary heart disease and diabetes mellitus type↑ in emergency workers of the Chernobyl accident

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Objective
The study was focused on evaluation of coronary heart disease (CHD) and diabetes mellitus type II (DM) onset in emergency workers (EW) who took part in elimination of the Chornobyl accident in 1986 year.
Materials and methods
The EW (n = 443, males) and 172 males not exposed to ionizing radiation (the control group, CG) were involved in the study in 2013–2019. EW absorbed doses of irradiation changed from 4.3 till 710 cGy. Diagnosis of CHD and type II diabetes mellitus (DM) was established in accordance with diagnostic standards of European Society of Cardiology and European Society of Endocrinology. All study subjects had no signs of CHD, and neither of endocrine disease nor of metabolic disorders before the accident.
Results
Patients that came in our hospital had cardiovascular diseases but comorbid diseases also analyzed. DM was diagnosed in 125 EW (28.2 %) and 42 persons (24.2 %) from CG. The onset of CHD was preceded by DM development in 40 (32.0 %) EW and 16 (38.1 %) CG patients. The DM course in EW was not significantly different from non-irradiated control by both severity and such complications as retinopathy, angiopathy of lower extremities and nephropathy; insulin was administered for no one patient. Concomitant DM was associated with a higher incidence of angina pectoris, heart failure and arterial hypertension equally in both groups. There were no significant correlation between absorbed dose and time of CHD or DM onset, as well as with age of these pathology developments. According to the Kaplan-Meier survival method, CHD developed in more young age than DM in EW (56.0 ± 0.4 vs 78.8 ± 0.9 years, log-rank test χ^2 = 402.8, P = 0.000) and CG patients (60.5 ± 0.7 vs 77.5 ± 1.2 years, log-rank test χ^2 = 135.5, P = 0.000). In EW the accumulation of new DM cases occurred faster in the EW compared with individuals of CG, however with statistical significance in subjects aged until 60 years old (log-rank test χ^2 = 4.99, P = 0.026).
Conclusions
Though the terms of CHD and DM onset did not depend on the radiation dose the labor under radiation exposure can be considered as a factor accelerating the development these diseases.
Keywords: chernobyl accident, radiation exposure, emergency workers, coronary heart disease, diabetes mellitus type.

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AEP1060

Risk factors for foot ulceration among adult patients with diabetes on chronic hemodialysis in Dakahlia governorate, egypt

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Background
Although risk factors for diabetic foot ulceration (DFU) have been extensively studied in patients with diabetes in Egypt, there is surprisingly limited evidence among those on chronic hemodialysis (CHD).
Aims
To investigate the risk factors for foot ulceration in adult patients with diabetes with end stage renal disease on hemodialysis in Dakahlia Governorate central hemodialysis units.
Patients and methods
This Cross-sectional study included all diabetic patients under CHD aged ≥ 18 years (n = 98), recruited over 7 months from the largest seven central hemodialysis units in Dakahlia governorate, Egypt. Dakahlia governorate has 18 central hemodialysis units. Data were collected on the following variables: age; gender; type and duration of DM; duration of dialysis, previous history of foot ulcers/ amputation, previous foot care education, and previous use of therapeutic footwear or custom made insoles (CMI). The feet were thoroughly examined, according to the International Working Group on the Diabetic Foot 2019 recommendations, to identify any deformities, skin or nail pathology, tenia pedis, or DFU. Footwear and foot health care behaviors were also assessed. Peripheral sensory neuropathy was detected using the 10-g (5.07 Semmes- Weinstein) monofilament. Peripheral arterial status was assessed by palpating the dorsalis pedis and posterior tibial pulses on both feet. The diagnosis of peripheral arterial disease (PAD) was further confirmed by measuring ankle pressure (Duplex; Bidop ES-100 V3 Hadeco Inc, Japan) and calculation of ankle-brachial index.
Results
The study included 57 males and 41 females. The mean age was 57.94 ± 8.93 years. The median duration of diabetes was 15 (2–33) years. 61 (62.2%) patients were on insulin therapy. The median duration of hemodialysis was 3 years. Insensate neuropathy was diagnosed in 65.3% of patients, and 15.3% of patients had PAD. The prevalence of foot deformities was 18.36%. Dry skin and plantar calluses were recorded in 62.2% and 27.6% of patients, respectively. Tinea pedis was found in 45.9%. 2 (2.04%) patients had active

foot ulcers, 9 (9.18%) patients had ulcers in remission; therefore the overall DFU prevalence was 11.22%. Ten patients (10.2%) had previous minor amputations, with no reported major amputations. 95.92% of patients had poor foot health care behaviors, and 81.63% were using inappropriate footwear. None of the included patients previously used CMI.
Conclusions
The key finding of this article suggests a high prevalence of risk factors for foot ulceration among diabetic patients receiving hemodialysis. Diabetic foot screening should be included in management strategy of those on CHD.
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AEP1061

The first case report of Pembrolizumab inducing thyroiditis and hypophysitis

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Pembrolizumab is a monoclonal antibody (ab) that exerts antineoplastic effects by inhibiting the immunoevasive effects PD-1 grants cancer cells. It's used to treat several forms of cancer, including melanoma and non-small cell lung cancer. Despite the promise pembrolizumab has demonstrated, it has been associated with immune-related adverse events. In this report, we describe the first case of both thyroiditis and hypophysitis occurring during active pembrolizumab therapy.
A 51-year-old male who was referred to endocrinology for subclinical hyperthyroidism. He has past medical history of hypertension, psoriatic arthritis, and poorly differentiated stage IV lung adenocarcinoma with brain metastasis. For the last 18 months, his cancer had been managed pharmacologically with pembrolizumab (200 mg every three weeks). The patient lacked a family history of thyroid disease and disclosed mild fatigue as his only symptom. Vital signs included the following: blood pressure of 92/42 mmHg, pulse of 68 beats/minute, respiratory rate of 16 breaths/minute, and body mass index of 29.94 kg/m^2. Physical examination was unremarkable. Pertinent laboratory test results included an elevated fT4 (1.6 ng/dl) and a suppressed TSH (< 0.005 µIU/ml). Thyroid stimulating immunoglobin, thyroid peroxidase ab, and TSH receptor ab tests were negative. Based on this work-up, the patient was diagnosed with pembrolizumab-induced thyroiditis and, given the mild presentation, was not prescribed anything.
At a follow-up visit two months later, the patient was found to have post-thyroiditis hypothyroidism, prompting levothyroxine initiation. After an additional four months, he complained of worsening fatigue and dry skin. TSH, fT4, FSH, LH, and total testosterone were within normal limits. 8 am cortisol, ACTH, free testosterone, and IGF-1 were reduced (0.7 µg/dl, 5.9 pg/ml, 6.1 pg/ml, and 37 ng/ml, respectively).ACTH stimulation test showed 0.5 mg/dl, 2.3 mg/dl, 3.1 mg/dl at morning, 30 and 60 minutes. A pituitary MRI was unremarkable. As a result, the patient was diagnosed with central adrenal insufficiency and started on hydrocortisone therapy. His condition improved with levothyroxine and hydrocortisone, and pembrolizumab was eventually discontinued after the patient switched to a new oncologist.
Hypophysitis occurs in approximately 1.1% of patients taking pembrolizumab. Pembrolizumab-induced thyroiditis is considered more common, though incidence estimates vary. Diagnosing these conditions involves clinical symptoms, laboratory test results, and imaging studies. With regard to imaging, pituitary MRI is the preferred study despite hypophysitis abnormalities appearing only 28% of the time. Finally, physician should keep hypophysitis diagnose in mind especially before starting patients on thyroid supplementation due to the chance of a frank adrenal crisis.
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AEP1062

The emotional outbreak of (endocrine) cancer patients during COVID-19 pandemic

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Background
The 2019 coronavirus disease (COVID-19) pandemic is a public health emergency and raises the issue of psychological and physical resilience in more vulnerable patients. We investigated the emotional impact of the SARS-CoV-2 spread among cancer patients, followed at our Institution in Italy, after the restrictive measures imposed by the government and the disruption of planned clinical activities.
Methods
From March 18th to April 1st, 2020, we conducted an online survey among cancer patients (Group 1: with advanced/metastatic disease undergoing systemic treatment; Group 2: with metastatic thyroid cancer in active surveillance; and Group 3: patients with no evidence of structural disease in standard follow-up), sending by email two questionnaires: the COVID-19 questionnaire,specifically designed by our team for the public health emergency ongoing, and an online version of the validated Italian translation of the EORTC QLQ-C30 questionnaire.
Results
The overall COVID-19 concernedness score was higher in women than in men (8 [IQR 5–9] vs 6 [IQR 5–8]; $P=0.048$), and in younger (<65 years) than in older ones (≥65 years) (8 [IQR 5–9] vs 6 [IQR 4–8]; $P=0.013$), without differences across cancer identified groups. The score had a strong inverse correlation with the EORTC QLQ-C30 Emotional function subscale (rho –0.69; $P<0.001$).
Conclusions
Patients with cancer (even if long-standing and well-controlled) report negative feelings and fear, independently from their actual need for medical care and from the seriousness of their disease. As physicians, we should reinforce patients' education and address all these worries, to provide the best possible high-value care.
Keywords: COVID-19,cancer care, quality of life, emotional outbreak
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AEP1063

Neuromyelitis optica presenting as intractable hiccoughs and SIADH: A Case Report

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Neuromyelitis Optica (NMO) is a neuro-inflammatory condition usually presenting with optic nerve and spinal cord events, caused by autoimmunity to Aquaporin 4 (AQ4) channels in the central nervous system (CNS). The high density of AQ4 channels in the hypothalamus and area postrema mean that NMO can occasionally present with atypical features. We present a 56-year old South Asian man, who presented with hiccoughs and Syndrome of inappropriate antidiuretic hormone (SIADH) and was eventually diagnosed with NMO.
Clinical Case
Patient presented with 3-day history of intractable hiccoughs; physical examination including neurological, was unremarkable. On admission, serum sodium was 123 mmol/l (135–145 mmol/l), urine sodium 61 mmol/l, urine osmolality 551 mosm/kg. Thyroid function tests, cholesterol and cortisol levels were within the normal range, suggesting SIADH. The CT Head was unremarkable; CT CAP demonstrated no evidence of malignancy. In the intensive care unit, hypertonic saline was administered, and he was fluid restricted. The serum sodium normalised, and he was discharged. He re-presented 2 weeks later with tingling and numbness to the left hand. He subsequently developed weakness in both upper limbs and dyspnoea. This time serum sodium was 137 mmol/l. CSF was acellular with normal protein and glucose with absent oligoclonal bands. Paraneoplastic serology was negative, however Aquaporin4 antibodies (AQ4Abs) were present. MRI Brain demonstrated a small focus of enhancement at the lateral aspect of the right ventricle and MRI Spine demonstrated a cervical cord lesion extending from the lower medulla to C7, with contrast enhancement suggestive of transverse myelitis. 18FDG PET imaging was normal. Intravenous methylprednisolone and plasma exchange were administered. He was started on mycophenolate mofetil and the prednisolone tapered. He improved clinically and follow-up scans demonstrated resolution of the cervico-medullary enhancement and reduction of the cord swelling.
Discussion
SIADH in NMO is attributed to targeting of the hypothalamic AQ4 channels by AQ4Abs. The intractable hiccoughs are associated with inflammatory involvement of the area postrema. The combination of SIADH and intractable

hiccoughs is rare, however both regions contain relatively high levels of aquaporin 4 channels and the combination should make clinicians strongly consider NMO even in the absence of the classical neurological symptoms.

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AEP1064

Pharmacokinetics and pharmacodynamics of macimorelin acetate (AEZS-130) in paediatric patients with suspected growth hormone deficiency (GHD)

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Growth hormone deficiency (GHD) in children is a rare, aetiologically diverse condition that results in growth failure and short stature. Inadequate response to two different growth hormone stimulation tests (GHST) is required for the diagnosis of GHD. Macimorelin acetate, a potent, orally administered growth hormone (GH) secretagogue, is approved by the FDA and EMA for the diagnosis of adult GHD. Study AEZS-130-P01 is the first of two studies to investigate macimorelin acetate as diagnostic test in children with suspected GHD. This was an open-label, group comparison, dose escalation trial to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of single-dose 0.25, 0.5 and 1 mg/kg oral macimorelin acetate in paediatric subjects with suspected GHD. The macimorelin GHST was administered between two standard GHST, conducted as per local clinical practice, with a recovery period of 7–28 days between tests. Blood samples were collected pre-dose (± 15 min) and 15, 30, 45, 60, 90, 120 and 360 minutes after macimorelin acetate intake. Overall, 24 paediatric subjects (8 per cohort [C1, C2, C3]) were included in the pharmacokinetic/pharmacodynamic (PK/PD) analysis. Five males and three females were observed in C1 and C2, seven males and 1 female in C3. In all three cohorts, at least 3 subjects represented Tanner stages I or II. All 24 subjects (100%) were white, with a median age of 9.8, 9.0 and 10.5 years (range 4–15 years) and a median body-mass index of 16.1 kg/m^2 (12.4–21.4 kg/m^2) at screening. Overall, 88 adverse events were reported, many related to the standard GHST; none were considered related to the macimorelin test. Maximum plasma concentrations for macimorelin were mainly observed between 30–45 min. The mean C_{max} values were 3.46, 8.13 and 12.87 ng/ml for C1, C2, and C3, respectively. The AUCs increased with dose; the mean $AUC_{0–6}$ values were 6.69, 18.02 and 30.92 h*ng/ml. The mean elimination half-lives were 1.22, 1.61 and 1.71 h, respectively. PK and PD profiles for all three cohorts were comparable, with peak GH levels mainly observed within 30–60 min following macimorelin intake. Macimorelin acetate was safe and well tolerated in all dosing cohorts. A dose-dependent increase in macimorelin C_{max} and AUC in children and adolescents correlated well with data from adultsubjects. A robust dose-proportional GH response was also achieved. PD results showed that GH response was comparable in all dose groups, with a slight shift to earlier t_{max} at higher macimorelin doses.

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AEP1065

Efficacy and safety of long-acting pasireotide in acromegalic patients in the real life: The reappraisal of the first-dose follow-up visit

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Background
Pasireotide is a multi-ligand somatostatin analogue licensed in a long-acting release formulation (PAS-LAR) for the treatment of acromegaly. The real-life reports with PAS-LAR are still scanty.
Objectives
To assess the efficacy and safety of PAS-LAR in patients with acromegaly.
Patients and methods
Prospective observational multi-centre study enrolling acromegalics evaluated before (baseline) and 1, 6, 12, 24, and 36 months after PAS-LAR start. Biochemical and radiological studies have been collected. Acromegaly symptoms and drug-related adverse events (AEs) have also been recorded. Patients achieving an IGF1-index (IGF1 normalised to the upper limit of normal) ≤1.3 were considered as controlled.
Results
forty-eight acromegalics were enrolled (22 females; mean age 43 years). All patients have been previously treated with first-generation somatostatin analogues. 77% of them had received multimodal treatments for acromegaly. The PAS-LAR starting dose was 40 mg/28 days in all and was escalated to 60 mg/28 days in 16 patients and decreased to 20 mg/28 days in 3. PAS-LAR significantly decreased IGF1-index levels (baseline vs the last visit: 1.9 ± 0.6 vs 1.2 ± 0.6, $P < 0.0001$) and controlled the disease in 62% of cases at last visit. Interestingly, the effects of PAS-LAR on IGF1 have been already observed during the 1-month visit (IGF1-index 1.4 ± 0.7, $P = 0.0002$ vs baseline; disease control rate 60%, $P < 0.0001$). Only minor changes were observed by carrying on the treatment and escalating the dose, not achieving a statistical significance. PAS-LAR was associated with a rapid improvement or disappearance of headache in 50% of the symptomatic patients even after the first drug dose. MRI showed a decrease in tumour volume in 44% of subjects and no changes in 56%. Hyperglycaemia was the most common adverse event of PAS-LAR. The prevalence of diabetes increased from 33% at baseline to 54% at the last visit. Three patients developed DKA. The second most frequent AEs was mild gastrointestinal discomfort. Most glycaemic and gastrointestinal AEs was recognised in the 1st-month visit or after dose escalation. Eleven patients had discontinued PAS-LAR mainly forlack of disease control or worsening of hyperglycaemia, both occurring in eight cases.
Conclusions
PAS-LAR significantly decreases IGF1 and the size of adenoma and may quickly improve headache in a significant percentage of acromegalic patients. The beneficial effects of PAS-LAR on IGF1 levels and headache as well as its glycaemic AEs may occur even after the first administration of the drug. The 1st-month evaluation should be considered part of the standard care of PAS-LAR treated acromegalics.

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AEP1066

Effect of long term rhgh treatment on bone mineral density in patients with childhood onset growth hormone deficiency

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Background
RhGH treatment in adults with childhood onset growth hormone deficiency (COGHD) affect bone metabolism over time according to gender and age. A long-term study of bone mass density (BMD) in young-middle age hypopituitary patients with COGHD may better highlight possible benefits of therapy and improve clinical follow up.
Methods
We enrolled 40 adults (age range during follow-up: 16.8–36 years, F: 38%) with COGHD with at least 20 years of clinical follow-up. The following data were collected at baseline and during the follow-up: anthropometric parameters,hormonal data, IGF-1 values, lumbar spine and femoral neck BMD derived from DEXA. Based on IGF-1 levels patients were divided into two groups: patients with continuous sufficient IGF-1 levels (at least 60% of IGF-1 values within the normal age and gender range) and patients with discontinuous IGF-1 levels (< 60% of IGF-1 values within the normal range).
Results
At lumbar spine,at baseline 47.5%of patients were osteopenic and 17.5% of patients were osteoporotic, these percentages did not differ during the follow-up. At femoral neck, 44.7% of patients were osteopenic and 2.6% were osteoporotic at study start and after 15 years of follow-up the percentage of osteopenic patients increased significantly while the others remained stable. Regarding BMD values, at lumbar spine there was a progressive increase of BMD up to 10 years of follow-up with a following reduction

and a return to baseline after 20 years (BMD g/cm^2: baseline 0.923±0.12, 10 years 0.991±0.13 *P* baseline vs 10 years<0.05, 20 years 0.924±0.15). At femoral neck there was no changes in BMD values up to 10 years, followed by a BMD deterioration below basal values after 20 years (BMD g/cm^2: baseline 0.797±0.14, 15 years 0.704±0.12 *P* vs baseline <0.05, 20 years 0.706±014 *P* vs baseline <0.05). Men had higher BMD than women at both sites. Patients with continuously sufficient IGF-1 levels had greater lumbar spine BMD levels compared to those with discontinuous IGF-1 levels (BMD IGF-1 in range vs IGF-1 below range: 10 years 1.009±0.14 vs 0.903±0.12 *P*<0.05, 15 years 0.948±0.11 vs 0.861±0.13 *P*<0.05, 20 years 0.975±0.12 vs 0.867±0.13 *P*<0.05), no differences were found in femoral neck BMD.

Conclusion

Our data supports the need for a punctual monitoring of bone metabolism and IGF-1 levels during prolonged rhGH therapy in GHD. Tostudy the long-term effect of GH replacement therapy on risk fracture in a rare condition such as GH deficiency, a multicenter study would be needed.

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AEP1067

Androgen deprivation therapy for prostate cancer with GnRH agonists: Metabolic consequences

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Objective

To assess metabolic disorders and thyroid function in patients with prostate cancer, who were treated with gonadotropin-releasing hormone(GnRH) agonist. Study design follow-up study.

Materials and methods

102 patients were enrolled to the study, 99 subjects were followed up till the study completion. The mean age was 69 years old (95% confidence range: 61.5–79.2 years old). To assess thyroid function, thyroid-stimulating hormone (TSH) and free T4 were measured prior to and in 12 months after androgen depriving therapy (ADT). To see metabolic disorders, waist circumference (WC), body mass index (BMI), and total cholesterol (TC) were measured prior to and 3, 6 and 12 months after ADT initiation.

Study results

The following changes were noted in test parameters: thyroid hormones (basic and 12 months later, respectively): TSH (mU/l): 1.67 506 and 1.90 684 (*P*<0.001), free T4 — 11.6266 and 11.0555 (*P*<0.001). Metabolic parameters (basic, 3, 6 and 12 months, respectively): WC (cm): 91.5, 95.4 (+4.2%), 96.1 (+5.0%), 96.4 (+5.4%) (for all differences *P*≤0.017); BMI (kg/m^2): 27.4, 28.2 (+2.9%), 28.4 (+3.6%), 28.4 (+3.6%) (*P*≤0.004 for all differences, save for differences between values in 6 and 12 months — *P*=0.995); TC (mmol/l): 5.2, 5.6 (+7.7%), 5.8 (+11.5%), 5.9 (+13.5%) (for all differences *P*≤0.001). Statistically significant positive correlation was recorded between TSH and TC dynamics (*R* v 0.285, *P*=0.004), statistically significant negative correlation — between TSH and free T4 (*R*=–0.315, *P*=0.001).

Conclusion

GnRH agonist monotherapy led to the trend of increase in WC, body mass, TSH raise and free T4 reduction one year after ADT, though mean hormone values were within acceptable range; TH demonstrated an increase. The highest increase in WC, BMI, TC was recorded within first 3 months of therapy, then the rate of increase diminished. Further study of metabolic and hormonal complications from ADT and evidence base enhancement are required in order to check the data and develop measures to prevent complications.

Keywords: prostate cancer, gonadotropin-releasing hormone agonist, thyroid function, metabolic disorders.

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AEP1068

Abstract withdrawn

AEP1069

The role of growth hormone device optimisation in patient-reported outcomes: Real-world evidence from South Korea

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Growth hormone (GH) therapy (GHT) requires long-term commitment to daily sc GH injections that may present adherence challenges. Patient preference and adherence have been shown to be affected by delivery devices in association with convenience of administration, level of injection-site pain, confidence in correct dose administration and satisfaction with the device. This survey investigated if switching GH device – from NordiLet/others to NordiFlex – improved patient-reported preference, satisfaction, ease of use and adherence in paediatric patients receiving GHT in South Korea. Patients aged 4 to ≤18 years receiving GHT from paediatric clinics in South Korea between January and July 2019 were surveyed. Participants were current users of NordiFlex for 4–24 weeks who had previously used NordiLet or other GH devices for≥12 weeks before switching. Patients/caregivers compared the subjective benefits of NordiFlex vs previous device in a 25-question survey comprising four domains: *ease of use*, *self-efficacy*, *minimal disruption of daily life*, *feelings about injections*. Patients responded on a 5-point Likert scale (−2 strongly disagree, −1 disagree, 0 no difference, 1 agree, 2 strongly agree). The survey also included questions about preference for, as well as satisfaction, perceived ease of use and self-reported adherence with, NordiFlex vs previous device. 94 patients were included in the survey. 91.5% previously used NordiLet; the rest used another device. Only 8.5% self-administered GH. A significantly greater proportion of patients preferred, and were more satisfied with, NordiFlex vs previous device; mean score: 0.65 (95% CI : 0.41; 0.88) and 0.61 (95% CI : 0.36; 0.85), respectively. Similarly, patients reported greater perceived ease of use and fewer missed injections with NordiFlex vs previous device; mean score: 0.49 (95% CI : 0.26; 0.72) and 0.20 (95% CI : 0.06;0.34), respectively. Bivariate analyses showed significant associations between the four domains and preference, satisfaction, perceived ease of use and self-reported adherence for NordiFlex vs previous device (*P*≤0.005). After multivariate analyses, higher scores of *ease of use* (adjusted OR [95% CI]: 3.77 [1.04; 13.57]; *P*=0.042) and *minimal disruption of daily life* (adjusted OR [95% CI]: 5.05 [1.09; 23.25]; *P*=0.038) were still significantly associated with preference for NordiFlex. However, associations with *self-efficacy* (adjusted odds ratio 1.10 [95% CI : 0.38; 3.21]) and *feelings about injection* (adjusted odds ratio 1.63 [95% CI : 0.44–6.01]) were no longer statistically significant (*P*>0.05). Patients reported greater preference, satisfaction, perceived ease of use and self-reported adherence with NordiFlex vs previous device, suggesting that improvements in injection device features could be associated with improved patient treatment experiences.

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AEP1070

Efficacy of lanreotide autogel for chinese patients with active acromegaly with or without prior pituitary surgery: A post hoc analysis of the Lantern study

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Background
Previous studies have yielded conflicting results on biochemical control with medical therapy in patients with or without prior pituitary surgery. The LANTERN study (NCT02493517) demonstrated that lanreotide autogel (LAN ATG) was non-inferior to lanreotide prolonged release (LAN PR) in Chinese patients with active acromegaly. This post hoc analysis of the LANTERN study aimed to explore the efficacy of LAN ATG in patients with or without prior pituitary surgery.
Design
Patients with active acromegaly were randomized to LAN ATG or LAN PR 40 mg for 32 weeks. This post hoc analysis focuses on the efficacy of LAN ATG in patients with (Group I) or without (Group II) prior pituitary surgery.
Results
There were 39 patients in Group I and 18 patients in Group II at Baseline. The median time since acromegaly diagnosis prior to Baseline was longer in Group I [median (Q1,Q3) 3.37 (0.90.4.02)] than Group II [0.44 (0.12.1.30) years; $P=0.001$]. Group I had higher age-adjusted mean Baseline IGF-1 standard deviation scores (SDS) than Group II (17.37±5.28 vs 13.65±6.11; $P=0.03$). Baseline GH level was comparable between Group I and II [10.37 (5.41.24.35) vs 18.84 (8.13.29.52); $P=0.226$]. Change in IGF-1 SDS from Baseline at Week 32 was –7.16 (95% CI 0.98.5.23) in Group I vs –4.96 (95% CI –7.84, –2.08) in group II ($P=0.218$). The proportion of patients achieving IGF-1 normalization at Week 32 in Group I (20.5%, 8/39) was almost twice that in Group II (11.1%, 2/18) ($P=0.622$). Change in GH levels from Baseline at Week 32 was comparable between Group I and II [–10.94 (95% CI –16.16, –5.71) vs –11.50 (95% CI –19.21, –3.78); $P=0.905$]. 28.2% (11/39) and 27.8% (5/18) patients in Group I and II attained GH levels ≤2.5 µg/L, respectively ($P=0.973$). Among patients with evaluable MRI both at Baseline and post-treatment, 39.4% (13/33) in Group I and 37.5% (6/16) in Group II achieved ≤20% reduction in tumor volume, respectively ($P=0.899$). The rate of treatment-emergent adverse events (TEAEs) was 94.9% in Group I and 88. 9% in Group II. The rate of severe and moderate TEAEs was lower in Group I (43.6%) than Group II (83.3%).
Conclusion
In the LANTERN study, patients with prior surgery had longer history of acromegaly and higher Baseline IGF-1 scores than those without. LAN ATG provided comparable biochemical control and tumor volume reduction in patients with or without prior pituitary surgery. The results indicate that prior pituitary surgery does not significantly affect the treatment efficacy and safety of LAN ATG.

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AEP1071

Outcomes of pituitary apoplexy: A comparison of microadenomas and macroadenomas

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Introduction
Apoplexy of pituitary microadenomas is rare and not well documented in the literature. We aimed to assess the clinical characteristics of apoplexy of pituitary microadenomas compared to that of macroadenomas.
Design
A single-center retrospective longitudinal cohort study.
Methods
We retrieved clinical records of patients over 18 years old, hospitalized in Rambam hospital (Haifa, Israel) between 1.1.2001–31.10.2017, with pituitary apoplexy confirmed by brain imaging (CT or MRI), and with a follow-up of at least one year. We compared clinical and biochemical outcomes of apoplexy among patients with microadenomas and macroadenomas. Statistical analysis was done using Fisher's exact and Mann-Whitney tests.
Results
We identified 40 patients hospitalized with pituitary apoplexy between 2001–2017. Twenty-seven patients had a follow up of at least one year and were included in the final analysis. Seven (26%) patients had microadenomas, 13 patients (48%) were female. The mean age was 40.7±12.5 years. Patients with microadenomas were younger than those with macroadenomas (29±5 vs 44±12 years, $P=0.006$). Median follow-up was 3 and 2.5 years for macro- and microadenoma groups, respectively. Twenty-one patients harbored clinically nonfunctioning pituitary adenomas (6/7 microadenomas and 15/20 macroadenomas). The hormonally functioning tumors were four macroprolactinomas, one microprolactinoma, and one growth hormone-secreting macroadenoma. Upon admission, hyponatremia, random cortisol level of <200 nmol/l and secondary hypothyroidism, were evident in 6/20, 8/18, and 4/18 patients with macroadenoma and in 1/5, 2/5, and 1/6 patients with microadenoma, respectively ($P=$NS). Hypogonadotropic hypogonadism was evident in 9/12 men with macroadenoma, but in none of the men with microadenoma. In 12 of macroadenoma patients, the tumor abutted the optic chiasm, of which eight had visual field defects. Fifteen patients with macroadenoma and two patients with microadenoma underwent transsphenoidal surgery within a median of four days. At the last follow-up visit, patients with microadenoma had lower rates of persistent corticotropic deficiency or secondary hypothyroidism compared to patients with macroadenoma (1/7 vs 13/20 respectively, $P=0.033$). The rates of persistent corticotropic deficiency or secondary hypothyroidism were comparable between patients that underwent surgery compared to patients that did not (10/17 vs 4/10, respectively, $P=$NS). 1/7 of patients with microadenoma and 3/20 with macroadenoma had persistent central diabetes insipidus ($P=$NS). Only 2 patients with macroadenomas had persistent visual field defects at the last follow-up visit.
Discussion
Long term pituitary hormone deficiencies are more common in pituitary apoplexy patients with macroadenomas. Apoplexy of pituitary microadenoma seems to carry a more favorable prognosis.

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AEP1072

Pregnancy outcomes in acromegaly: A single tertiary center case series

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Introduction
Pregnancy occurs relatively rare women with acromegaly. However, in recent years, pregnancy has become more likely to occur in acromegalic women possibly due to improvements in acromegaly treatment, and advanced assisted reproduction techniques.
Methods
In this case series, we retrospectively analyzed 11 pregnancies of 8 acromegalic women followed in the university hospital in a time range between 2009–2019. Data were obtained from patient files.
Results
The median age at the time of acromegaly diagnosis was 25.5 years (range: 18–29 yrs). All patients had macroadenoma at the time of diagnosis with a maximum median diameter of 22 mm. Surgery was the primary choice of treatment in all patients. Four women had a history of radiotherapy. The median duration of time between pituitary surgery and conception was 7 years, while acromegaly was diagnosed at the 12th month of lactation from previous delivery in one patient. The median GH and IGF-1 levels at the last visit before the detection of pregnancies were 1.5 ng/ml and 307 ng/ml respectively, and the median maximum diameter of residual pituitary adenoma was 6 mm. Only five out of 11 pregnancies were planned. Three of the five planned pregnancies occurred spontaneously while two occurred with *in vitro* fertilization. One patient was able to become pregnant at the third attempt of *in vitro* fertilization. In acromegalic women planning pregnancies, somatostatin analogs ($n=5$) treatment were discontinued 17 months before conception. Six unplanned pregnancies occurred while patients were on somatostatin analogs ($n=6$) treatment. Three out of six unplanned pregnancies reached term while two were terminated due to octreotide use, and one resulted in spontaneous abortion in the first trimester. Also one out of five planned pregnancies ended in the first trimester due to spontaneous abortion. No complications such as gestational diabetes and preeclampsia were observed in seven pregnancies reaching term, cesarean section being the method of delivery in all. No congenital anomaly was observed in the babies. Increase in adenoma size of one mm was noted in one patient only. Lactation did not occur after one out of these seven pregnancies.
Discussion
There is no consensus on the follow-up of pregnancies in women with acromegaly. It is usually recommended to discontinue medical treatment as soon as pregnancy is detected. Although a majority of pregnancies occurred in acromegalic women are reported to reach term without major complications, particular attention should be paid to these women regarding gestational diabetes, hypertension and apoplexy.

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AEP1073

A randomized-controlled trial of tesomet resulted in significant weight loss in hypopituitary patients with hypothalamic obesity

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Background and objective
Hypothalamic obesity is characterized by rapid and severe weight-gain with increased risk of cardiovascular and metabolic disorders. Currently, there are no approved or effective pharmacological treatments and conventional weight management remain largely ineffective in hypothalamic obesity. This trial investigated safety and efficacy of Tesomet (0.5 mg tesofensine and 50 mg metoprolol) in hypopituitary patients with hypothalamic obesity.
Methods
Twenty-one (16 females) hypopituitary patients with hypothalamic obesity were randomized double blinded 2:1 to receive daily Tesomet or placebo for 24-weeks (NCT03845075). All subjects received diet- and lifestyle counseling for weight management. The primary endpoint was safety based on heart rate, blood pressure and adverse events. Secondary endpoints included antropometrics, metabolic and pituitary hormone replacements The median age of subjects was 50 years [range 25–70], 52% had BMI 30 kg/m^2, and 38% BMI>40 kg/m^2. Almost half had a history of craniopharyngeomas, 86% had undergone pituitary/hypothalamic surgery, 52% irradiation. All patients received one or more anterior pituitary hormone replacements; 52% had diabetes insipidus.
Results
Four subjects, two in the placebo- and two in the treatment-group, discontinued treatment before the end of the 24-week period. Discontinuation in the treatment arm was secondary to anxiety ($n=1$) and dry mouth ($n=1$), both improved after drug discontinuation. Adverse events were otherwise mild to moderate and included sleep disturbances (62%), dry mouth (46%), dizziness (46%) and headache (38%), known side-effects of tesofensine or metoprolol. No significant differences in heart rate or blood pressure were observed between the two groups. Eighteen of the 21 patients completed the 24-week placebo-controlled part of the study. Compared with placebo (weight loss 0.3%), Tesomet treatment resulted in an additional mean [95%-CI] weight loss of 6.3% [1.3%, 11.3%] at week 24 ($P=0.017$); a significant increase in the proportion of patients with 5% reduction in body weight (Tesomet $n=8$; 61.5%; placebo $n=1$; 12.5%) ($P=0.046$); a significant reduction in waist circumference at week 16 and 20, approaching significance ($P=0.052$) at week 24 with a mean reduction of 5.0% [0.1%, 10.1%]. Odds-ratio of subjects achieving 5% weight loss compared with placebo was 11.2 [1.0–120.4] ($P=0.046$).
Conclusion
Tesomet treatment was generally well tolerated, did not affect heart rate or blood pressure and resulted in additional significant progressive reductions in body weight and waist circumference compared to placebo in this small cohort of hypopituitary patients with hypothalamic obesity, all receiving the same dietary guidance. These results support the continued development of Tesomet for hypothalamic obesity.

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AEP1074

ACROCOVID: An international survey on care for acromegaly during the COVID-19 era

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The COVID-19 pandemic is significantly affecting the care of chronic conditions globally. Acromegaly is a rare chronic condition with a prevalence ranging between 2.8–13.7 cases/100.000 people. Acromegaly management requires a multidisciplinary team of health care professionals (HCPs), mainly including endocrinologists, neurosurgeons, and specialized endocrine nurses. Frequent consultations, particularly during early stages of the disease, and pre/post-surgery are necessary. Furthermore, injectable somatostatin receptor ligands may require HCP support to administer, while the need for blood-test monitoring necessitates adequate laboratory provisions. All of the above treatment considerations are likely to be impacted during the current pandemic. With median diagnosis occurring during the 5th decade and a high risk of cardiovascular and respiratory diseases, the majority of people with acromegaly are likely to be at a greater risk of severe illness if infected with SARS CoV-2. Although acromegaly itself doesn't increase risk of infection, people with adrenal insufficiency on glucocorticoid replacement may be at a higher risk. Expert opinion on pandemic-concurrent management of acromegaly has been published, but the real-world impact of COVID-19 has not been established. Decreased quality of life and psychological symptoms, including apathy, blunted affected and depressed mood, are a common feature of acromegaly. The socio-behavioural measures put in place in order to control the pandemic have the potential to exacerbate these issues through the disruption of routine social and work-related activities. In addition, access to resources for vulnerable members of society may be complicated by the fact that acromegaly can often be an 'invisible disability'. In order to assess the myriad effects of COVID-19 on people with acromegaly and their HCPs, we aimed to conduct an international online survey. The survey is tailored to four audiences: people with acromegaly; endocrinologists; specialized endocrine nurses; and neurosurgeons. The survey for people with acromegaly will focus on five broad categories of questions: impact on day-to-day life; access to HCPs; access to treatment and testing; impact on emotional and financial functioning; and future management. Questions in the HCP surveys will focus on five broad categories: impact on evaluation and diagnosis; access to treatment and management; impact on monitoring; role of technology and remote communication; and future management. Development and completion of the surveys has been achieved through patient and physician specialized societies. Complete analysis will be presented at eECE 2020. Successful multidisciplinary care models implemented during this pandemic could add valuable experience for future care for people with acromegaly and physicians alike.

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AEP1075

COVID-19 and hypopituitarism. Experience from an endocrine center in a high-impact area

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SARS-CoV-2 has rapidly spread from China throughout the world leading to a pandemic. COVID-19 can be severe enough to cause hospitalization and death. Many patients with endocrine disorders share many of the recognized risk factors for severe disease and have potential additional risks due to corticosteroid replacement therapy or alteration in blood electrolytes. We here report three cases of COVID-19 in patients with post-surgical hypopituitarism and documented hypocortisolemia. An 80 yr-old patient with hypopituitarism and diabetes insipidus after surgery for craniopharyngioma in 1990, tested positive for Sars-CoV-2 at hospital admission for cardiogenic syncope. He suffered of hypertension, mild diabetes, COPD, atrial fibrillation, vascular disease; he was on stable therapy with L-T4, high dose cortisone acetate (62.5 mg/day), intranasal desmopressin and anticoagulants. He had no symptoms nor radiological signs specific for COVID-19.Blood tests showed hyponatremia (Na^+ 128.3 mmol/l) and increased LDH (290 U/l), CRP (82 mg/l, RR. <6), IL6 (262 pg/ml, RR. <7) and D-dimer (>20 mg/ml, RR. 0.27–0.77). He received a supplemental dose of parenteral hydrocortisone, optimization of desmopressin and no specific therapy for COVID-19. He was discharged after placement of a pace-maker. A 78 yr-old male patient with hypopituitarism after surgery for suprasellararachnoid cyst was on stable therapy with L-T4, cortisone acetate (25 mg/day), testosterone and growth hormone. He presented to the ER with cough, dyspnea and fever for one week. He tested positive for Sars-CoV-2; chest CT showed COVID-19 associated pneumonia. Mistakenly, cortisone acetate therapy was missed for 40 hours while staying in ER. Blood tests showed hyponatremia (Na^+129 mmol/l) and increased LDH (230 U/l) and CRP (53 mg/l). He received low-flux oxygen, ritonavir/lopinavir and hydroxychloroquine. His clinical conditions significantly improved and he was discharged after 6 days. An 18 yr-old male with hypopituitarism after surgery for craniopharyngioma at 12 yo, severe obesity (BMI 49.5), diabetes insipidus, was on stable therapy with L-T4, hydrocortisone (25 mg/die), desmopressin, testosterone and growth hormone. He presented to the ER with fatigue and drowsinessand no respiratory symptoms. He tested positive for Sars-CoV-2. Chest X-rays showed an increase of vas-

cular pattern in both lungs. Blood tests showed increased CRP (25 mg/l), normal IL6 and D-Dimer. He received antibiotic therapy and prophylactic anticoagulant coverage with LMWH; oral hydrocortisone was doubled. No respiratory complications occurred and the patient was discharged 3 days later. In conclusion, patients with hypopituitarism may be more susceptible to COVID-19 although severity of the disease does not seem to be increased.

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AEP1076

Outcome squares integrating efficacy and safety, as applied to functioning pituitary adenoma surgery

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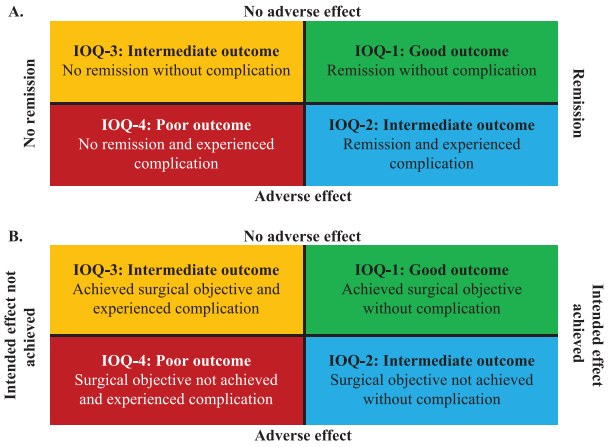
Background
Transsphenoidal surgery is standard care in the treatment of hormone-secreting pituitary adenomas. Current clinician-reported surgical outcome measures are one-dimensional, typically focussing primarily on complete or partial resection and secondarily on complication rates. However, outcomes are best reflected by the delicate balance of efficacy and complications at patient level. This study proposes a novel way to classify outcome, integrating efficacy and safety at the patient level.
Methods
Retrospective chart review of all pure endoscopic transsphenoidal surgical procedures for acromegaly, Cushing's disease, and prolactinoma between 2010–2018 in a single tertiary referral centre. We present our results in a classic (remission and complications separate) and in a novel Outcome Square integrating intended and adverse effects (long-term complications). This resulted in four outcome groups, ranging from good to poor. We use this approach to present these outcomes for several clinically relevant subgroups.
Findings
198 surgical procedures were included (44 reoperations). Remission was achieved in 127 operations (64%). Good outcome was observed after 121 (61%), and poor outcome after 6 (3%) operations. When intended effect of surgery was applied (instead of remission), good outcome was achieved after 148 of 198 surgeries (75%) and poor outcome after 4 (2%).
Interpretation
Quality of a surgical intervention can be presented in 4 simple categories, integrating both efficacy and safety with flexibility to adapt to the individualized situation at patient, disease, and surgical strategy. Funding. No specific funding was received for this research

Table 1 Construction of the Outcome Square, a contingency table integrating efficacy with safety. Definitions of remission, intended effect and adverse effect are provided in the methods section. IOQ: integrated outcome quadrant (1–4).



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AEP1077

Pituitary apoplexy in the elderly: About 3 cases

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Introduction
Pituitary apoplexy is a rare clinical syndrome related to abrupt hemorrhage and/or infarction of the pituitary gland,usually occurring in patients with pre-existing pituitary disease. it is an endocrine emergency requiring rapid diagnosis and appropriate management.
Observation
We report the observation of three patients.
Case 1
This is a 72 year old patient, without any particular pathological history, who presented abruptly a ptosis of the left eye without tumour syndrome, without sensory-motor deficit associated with asthenia worsening at the end of the day, without signs of hypersecretion of the pituitary gland. Total paralysis of the left oculomotor nerve was noted. MRI showed a bleeding pituitary macroadenoma and laterosellar macroadenoma. Blood hypophysogram showed thyreotropic and corticotropic insufficiency. The patient benefited from transphenoidal excision of the tumour. The evolution was favourable, marked by the regression of ptosis after orthoptic rehabilitation. The anatomopathological study showed a non-secreting pituitary macroadenoma.
Case 2
This is an 87 year old patient admitted for afemoral neck fracture, who presented an ante-pituitary insufficiency made of asthenia without tumor syndrome or pituitary secretion syndrome and the questioning finds a notion of intense headaches for several months. The hypophysogram showed a corticotropic and thyroidotropic deficit that we substituted and a decrease in gonadotropins (FSH, LH).MRI showed a necrotic suprasellate-extension pituitary macroadenoma.
Case 3
An 82-year-old patient was admitted with severe headache and vomiting associated with paralysis of the common oculomotor nerve, without pituitary secretion syndrome. Blood hypophysogram showed a corticotropic deficit which we substituted and a decrease in gonadotropins (FSH, LH). The MRI objectified a hemorrhagic pituitary macroadenoma in favor of a pituitary apoplexy. As surgery was contraindicated in the last two patients because of their medical issues, we opted for medical treatment.
Discussion
Pituitary apoplexy is an endocrine emergency. A rapid diagnosis and appropriate management can limit the occurrence of irreversible complications. These observations illustrate the particularities of this pathology in the elderly, the symptoms may be truncated and lead to a late diagnosis with its repercussions on management, without forgetting the particularity of the fragile and multi-systemic terrain which may contraindicate the usual surgical treatment.

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AEP1078

First results of a desmopressin test in forecasting of relapse acth-dependent cushing syndrome undergoing tss

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Hypercorticism is a syndrome caused by extended and very high exposure of glucocorticoids to the body. ACTH-dependent Cushing's syndrome develops as a result of the overproduction of adrenocorticotropic hormone by the pituitary adenoma. The main treatment for ACTH-dependent Cushing's is transnasal transsphenoidal removal of the pituitary adenoma. A the same time, the recurrence rate of Cushing syndrome is observed up to 3% during the year and up to 3%–22% of cases within 3 years. The test with the introduction of desmopressin(TD) after surgery along with other samples to determine the presence of residual neoplastic corticotrophs, that is, an increased risk of reccurence.
Objective
to analyze the prognostic value of aTD to assess the effectiveness of TSS in patients with ACTH-dependent CS in the postoperative period
Material and methods
42 patients with ACTH-dependent Cushing's syndrome were examined, operated on in the neurosurgery departments of the RSSPMCE from 2000 to 2019. Patients were divided into 2 groups: 1 gr had cortisol levels ≤138 nmol/l (18patients), and group 2 (24 patients) had cortisol levels

≥138 nmol/l in the first 1–3 days after transsphenoidal pituitary adenomectomy (TSS). The control group consisted of 20 healthy individuals of a similar age. The research methods were general clinical, instrumental,hormonal, functional test with desmopressin and statistical methods
Results
It was found that in the group of patients in remission, in 3 patients ACTH levels during desmopressin test increased significantly (on average 14.02±2.06 ng/dl), leading to a corresponding increase in the level cortisol (average 280.02±12 nmol/l) in the blood. Moreover, the peak of ACTH secretion was accounted for and held equally high at 301 and 601. As the test results show, the averaged ACTH and cortisol indicators in group I differed from the control group, although not significantly ($P>0.05$). While, a significant reaction was noted in response to desmopressin, which increased 4 times more than in the control group. In the second group, 6 patients out of 24 of patients had a positive reaction to desmopressin, as evidenced by an increase in cortisol levels and which can serve as a negative prognostic marker of the probability of a relapse.
Conclusions
Thus, according to the initial results of our studies, analysis of the results of the desmopressin test in patients withACTH-dependent Cushing's syndrome showed that desmopressin test is a sensitive tool in determining the reactivity of corticotrophic pituitary cells.

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AEP1079

The histological structure of giant non functional pituitary adenomas with invasive growth

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Aim of the research – to study the histological structure of non functional pituitary giant adenomas (NFPA).
Materials and methods
We observed 17 patients with giant NFPA, among them 5 male and 6 female, mean age 37.8. All patients were undergone surgical treatment by transsphenoidal access in Center of Endocrinology of MoH RU in neurosurgery department during 2019–2020 year. All patients were undergone the spectrum of analyses, including endocrine status assessment, clinical, biochemical, hormonal (GH, LH, FSH, prolactin, TSH, testosterone and others), radiological (CT/MRI of Turkish saddle), and histological study. All patients have pituitary adenoma more than 3 cm. Depending on the type of cells found on the histological study, patients with NFPA (chromophobic adenomas) were divided into 3 groups: 1st group – small cell (undifferentiated) chromophobic adenoma – 7 patients, 2nd group – large cell chromophobic adenoma – 8 patients, and 3rd group – oncocytoma (none)- 2.
Results
Preliminary analysis of the research showed that among the observed patients the most disposed to invasive total growth had patients of the 1st group with small cell histological structure of NFPA. Besides, this patients had more frequent tumor relapse in post-operative period – 3 patients (17.6%), had acute manifestation of the disease with general cerebral symptoms and neuroendocrine disturbances (secondary amenorrhea in female, potency and libido decrease in male, metabolic syndrome, visual disturbances and others). Two female patients aged 27.5 from the 1st group were undergone repeated selective pituitary adenomaectomy 3 times.
Conclusions
1. Small cell NFPA have the most aggressive growth and tumor relapse. 2. Following research is necessary to study the markers of aggressiveness in all 3 groups.

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AEP1080

Gender differences of growth hormone and insulin-like growth factor-1 in patients with acromegaly after radiation therapy

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Purpose of the study
To determine the gender differences in growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in patients with somatotropic pituitary adenomas after radiation therapy (RT).
Materials and research methods
The object of the study is 94 patients with acromegaly receiving RT in a total dose of 45–50 gray. Of these, 26 (27.7%) are men and 68 (72.3%) are women. The peak manifestation of acromegaly in the total sample was in the most able-bodied age for men and women (30–44 years old). Conducted hormonal, visualization, ophthalmologic, general clinical research.
Results
The level of GH before RT was increased in men 55 (37.6–81.3) mMe/l and in women 59.3 (43.3–110) mMe/l. After RT, the level of GH in men in 15.4% ($P<0.01$) of cases is not suppressed, not completely suppressed in 34.6% ($P<0.05$), reached remission of 50% ($P=0.001$) and amounted to 11 (4.15–15.3) mMe/l. In women, 22.1% ($P<.05$), 17.7% ($P<0.01$) and 60.3% ($P=0.001$), respectively, and averaged 5.8 (2.4–15.3) mMe/l. Prior to RT, IGF-1 levels in men were 767 (619–962) ng/ml and in women 784 (678–1113) ng/ml. The levels of IGF-1 after RT in men were not suppressed in 46.2% ($P<0.01$), suppressed to age norms in 53.9% ($P<0.001$) and averaged 257 (200–299) ng/ml, in women, in 39.7% ($P<0.05$) and 60.3% ($P<0.001$), respectively, it amounted to 207 (181–308) ng/ml.
Conclusion
Thus, despite the high levels of GH and IGF-1 before RT in women than in men, women achieved remission more often and had lower levels of IGF-1 and GH compared with men.

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AEP1081

Efficacy of lanreotide autogel in Chinese patients with acromegaly according to tumor size: A post hoc analysis of the LANTERN study

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Background
The LANTERN study (NCT02493517) has demonstrated that lanreotide autogel (LAN ATG) was non-inferior to lanreotide prolonged release (LAN PR) in Chinese patients with active acromegaly. This post hoc analysis of the LANTERN study assessed the impact of tumor size on treatment effect.
Design
In the LANTERN study, LAN ATG was started at 90 mg and subsequently titrated according to GH and IGF-1 levels for 32 weeks. Tumor diameters >10 mm were classified as macroadenoma (Group I) and ≤10 mm as microadenomas (Group II) using centralized blinded review of magnetic resonance imaging (MRI) scans. This post hoc analysis focuses on the efficacy of LAN ATG in Group I vs Group II.
Results
There were 38 patients in Group I and 14 patients in Group II. Group I had higher Baseline GH level than group II [median (Q1,Q3): 21.57(8.05, 32.06) vs 6.02 (4.27, 15.02); $P=0.004$]. Meanwhile, mean Baseline age-adjusted IGF-1 SDS was comparable between Group I and Group II [15.76±6.20 vs 13.67±6.17; $P=0.285$]. For change from Ba seline at week 32, GH levels decrease in Group I was approximately half of that in Group II [–9.39 (95% CI –14.89, –3.88) vs –16.48 (95% CI – 25.77,–7.19); $pw=0.202$]; IGF-1 SDS score decrease was significantly lower in Group I than in Group II [–4.95 (95% CI –6.81, –3.10) vs –10.01 (95% CI –13.09, –6.94); $P=0.007$]. Furthermore, a lower proportion of patents in group I attained GH level ≤2.5 µg/l vs Group II (13.16%, 5/38 vs 50.00%, 7/14, $P=0.015$); a smaller proportion of patients in Group I achieved normalized IGF-1 levels than in Group II (7.9%, 3/38 vs 35.7%, 5/14; $P=0.042$). In patients with evaluable MRI results both at Baseline and post-treatment, 36.1% (13/36) patients in Group I achieved≥20% reduction in tumor volume vs 46.2% (6/13) in Group II ($P=0.524$). The rate of treatment-emergent adverse events (TEAEs) was 94.7% in Group I and 92.9% in Group II. The rate of severe and moderate TEAEs was 57.9% in Group I and 50% in Group II. No treatment-emergent deaths were reported.
Conclusion
In this post hoc anaylsis, LAN ATG provided similar reductions in tumor volume≥20% in patients with acromegaly regardless of tumor size(i.e. marcoadenoma or microadenoma). Biochemical control appeared to be better in

patients with microadenoma than in those with macroadenoma, potentially due to imbalance in Baseline GH levels between the two groups. The safety profile of LAN ATG was consistent with previously reported data.

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AEP1082

Somapacitan dose–IGF-I–response and impact of starting dose levels in adults with growth hormone deficiency – a model-based analysis

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In patients with adult growth hormone deficiency (AGHD), the dose of growth hormone (GH) replacement is individualised based on clinical outcome, insulin-like growth factor-I (IGF-I) levels and adverse reactions. The aim of this analysis was to characterise dose–IGFI–response for somapacitan, a long-acting reversible albumin-binding GH derivative, and to derive expected IGF-I levels for various starting doses. Somapacitan dose–IGF-I–response analysis was conducted in 330 patients with AGHD across three phase 3 trials; GH treatment-naïve patients (NCT02229851), and patients previously treated with GH (NCT02382939, NCT03075644) were analysed using a population pharmacokinetic/pharmacodynamic (PK/PD) model. Dose titration was performed with starting doses of 1.5 mg/week, 1.0 mg/week, and 2.0 mg/week, respectively, for patients ≤60 years old, >60 years old, and female patients taking oral oestrogen. The impact of demographic covariates (weight, sex, oral oestrogen, age and race [White/other, Asian Japanese, Asian non-Japanese]) upon PK/PD parameters was investigated. Individual PK/PD parameter estimates were used to derive average IGF-I standard deviation score (SDS) at the fixed dose level after titration, and for each individual across the 0.1–8.0 mg/week dose range. Age, sex and oral oestrogen use were the most influential covariates on somapacitan dose–IGF-I–response. Higher doses of somapacitan were required to reach similar IGF-I targets in female patients, particularly those taking oral oestrogen, compared with male patients. Lower doses were required to reach similar IGF-I targets in >60 vs ≤60 year old patients. Race and body weight did not alter somapacitan dose–IGF-I–response. Mean fixed somapacitan dose after titration was 2.1 mg/week, 1.4 mg/week and 3.8 mg/week, respectively, for patients ≤60 years, >60 years, and female patients taking oral oestrogen. Based on PK/PD analysis, investigated starting doses of 1.5, 1.0 or 2.0 mg/week would result in a mean IGF-I-SDS of –0.4, with approximately 1% and 10% of patients with IGF-I-SDS >2 and <–2, respectively. Starting doses of 2.0, 1.5 or 4.0 mg/week, would result in a mean IGF-I-SDS of 0.1, with approximately 5% of patients with IGF-I SDS >2, and 5% with IGF-I-SDS <–2. This approximates the distribution of IGF-I levels in the healthy population. In conclusion, this PK/PD analysis suggests that a starting dose of 1.5 mg/week (1.0–2.0 mg/week) of somapacitan is expected to produce an IGF-I SDS in the lower range of normal, and provides an insight into the theoretical impact of higher starting doses.

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AEP1083

Monitoring of weekly IGF-I levels during long-acting growth hormone therapy with somapacitan

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Somapacitan is a long-acting growth hormone (GH) derivative designed for once-weekly subcutaneous administration. Correct assessment of insulin-like growth factor-I (IGF-I) levels is essential during treatment of GH deficiency (GHD) and must account for fluctuations over a dosing interval. We evaluated whether reliable estimates of weekly mean and peak IGF-I could be obtained from a single IGF-I sample. A population pharmacokinetic/pharmacodynamic model was available from pharmacokinetic and IGF-I (ng/ml and standard deviation score [SDS]) profiles from phase 1 studies of healthy adults (NCT01514500), adults with GHD (NCT01706783) and children with GHD (NCT01973244). Simulation was performed to steady state at four dose levels for 26 adults (doses 0.02–0.12 mg/kg) and 23 children (0.02–0.16 mg/kg) with GHD. After 200 repetitions, 39.200 unique IGF-I profiles were simulated using a 4-hour grid from 0–168 hours after dose. Profiles with weekly average IGF-I SDS >4 were removed. For each potential sample time, a linear model was used to estimate the correlation between IGF-I SDS value at a given time and the weekly mean/peak IGF-I value. The best fit to data included a dose (mg) covariate with body weight as an interaction in adults and a logarithmic dose level (mg/kg) covariate in children. The degree of linearisation was evaluated with correlation coefficient R^2, and precision of weekly mean/peak predictions were evaluated using residual standard deviation (RSD) and 90% prediction interval (PI; calculated as ± 1.645*RSD). Strong linear correlations were found between IGF-I SDS on any day and the weekly mean across the dose ranges, as well as between IGF-I SDS on days 1–5 and the weekly peak. In children and adults, the mean was predicted with good precision based on an IGF-I sample on any day (RSD < 0.4 for adults; < 0.3 for children); the most accurate prediction was on day 4 (RSD < 0.17 [90% PI ± 0.3 SDS]). The peak was best predicted with an IGF-I sample on days 1–4 (RSD <0.4); the most accurate prediction of IGF-I peak was on day 2 (RSD < 0.10 [90% PI ± 0.2 SDS]). A linear model provided a simple and reliable tool to predict weekly mean and peak IGF-I levels based on an accurate IGF-I sample following somapacitan dosing at steady state. Mean and peak IGF-I values could be predicted by IGF-I sampling on any day after somapacitan dose. The best predictive values were on day 4 (mean) and day 2 (peak) after dose.

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AEP1084

Diagnostic of erdheim chester histiocytosis 9 years after!

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Erdheim Chester disease (ECD) is a non langheransian rare histiocytosis, with around 500 cases described worldwide since its discovery for the first time in 1930 by Jakob Erdheim et William Chester. It is a multivisceral disease, characterized by a proliferation of abnormal histocytes CD68 positive and CD1a negative, including a retroperitoneal and perirenal fibrosis, a peri-aortitis, an osteosclerosis of the lower limbs and sometime an exophthalmia or an diabetes insipidus. However, cases may be non-typic and confusing. We report the case of the patient B.K aged of 31 years old, followed for diabetes insipidus with an enlarged pituitary stalk evolving for 10 year, posing an etiological diagnostic problem. Sarcoidosis have been first discussed without à lot of arguments, conducing to the introduction of corticotherapy, with a morphological response (regression of the stalk enlargement on the IRM). The patient has been regularly followed and 9 years after, an expansion of the pituitary stalk led us to reevaluate him. A thoraco-abdominal CT has found a retroperitoneal infiltration (peri-pancreatic) which helped us to discuss Erdheim Chester disease. Bone scintigraphy has found multiple fixations on long bones of the lower limbs. A cutaneous localization as a xanthélasma on the lower eyelids is describe with recurrent outbreaks of headache with fever. The diagnosis of certainty was obtained by an immunohistochemical study on biopsy of the bone marrow, finding squamous histocytes expressing CD68, weakly PS100, without expression of CD1a and nuclear expression of D1 cylinder. We have introduced an antagonist interleukin 1 receptor (Anakinra) with a good clinic-biological response. The etiologic diagnostic of a pituitary stalk enlargement is often complicated, it is essential to maintain a clinical and morphological follow-up and discuss rare disease as Erdheim Chester histiocytosis.

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AEP1085

The course and predictors of postoperative diabetes insipidus

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The course and predictors of postoperative diabetes insipidus.
Objectives
To evaluate the course and predictors of permanent and transient postoperative diabetes insipidus (DI).
Patients and methods
The study included 152 patients undergoing endoscopic endonasal transsphenoidal surgery aged from 18 to 65 years with median 40. 73 patients had Cushing disease, 66 – acromegaly, 4 – prolactinoma, 9 – hormonally inactive adenoma, 1 – Nelson syndrome, 1 – TSH-oma. Patients were mon-

itored for hormones, serum electrolytes, plasma and urine osmolality. The follow-up period extended over 6 years for 97 patients and 55 patients (36%) had been lost to follow-up.
Results
In 34 patients (22.4%) postoperative DI was diagnosed by discharge, among them in 16 patients disturbances later became self-limited. Self-limited disturbances occurred in 25 patients (16.4%) when discharged, among them, permanent DI occurred in 3 patients during follow-up. 91 patients did not have any disturbances when discharged but permanent DI occurred in 1 patient and transient – in 8 patients during follow-up. By the end of follow-up period, permanent DI has developed in 15 patients (15.5%), transient – in 34 (35.1%). The onset was seen on the median 5th day [1; 9.5] after surgery for the permanent DI and on the 1th median day [1; 4.5] for transient; median for transient DI's duration was 30 days [1.5; 195]. When assessing the level of osmolality and sodium, the indice of serum sodium in patients with a transient DI was significantly higher in comparison with patients without disturbances. In patients with a constant and transient DI the indices of urine osmolality and urine specific gravity were significantly lower compared to patients without disorders and sodium urine indices were significantly higher. The transient DI occurred more often in patients with corticotropinomas in comparison with other pituitary adenomas (OR 6.1 (2.3;16.1)) and in patients with microadenomas (OR 5.3 (2.0;14.2)). Adrenal insufficiency increased risk of transient DI development (OR 6.8 (2.6;18.3)) and secondary hypothyroidism – of permanent DI (OR 9. 8 (2.1;46.6)) comparing to patients without hypopituitarism. Pituitary excision increased risk of permanent DI development as well (OR 4.9 (1.3;17.6)).
Conclusions
The diagnosis of permanent or transient postoperative DI should be specified after a long-term follow-up. The onset of postoperative DI arises on the 1–5 day after surgery and rapidity of recovery varies wildly. Cushing disease, pituitary microadenomas and adrenal insufficiency can be considered as predictors of transient DI, secondary hypothyroidism and pituitary excision can be considered as predictors of the permanent postoperative DI.

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AEP1086

Influence of radiation therapy on patients with acromegaly depending on the age of patients

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Aim
To evaluate the effectiveness of radiation therapy (RT) in patients with acromegaly, depending on the age of patients and the activity of pituitary adenomas.
Materials and methods
The subject of the study were 50 patients (women-36, men-14) with acromegaly who received gammatherapy in a total dose of 45–60 Gr of 20–25 fractions every other day. The duration of the disease was 15 years on average. In general, the age of patients ranged from 26 to 77years, on average-44.7±6.8 years. By age, the patients were divided into 3 groups: the I age group-29–44 years-23 patients (46%), the II group-45–59 year-16 patients (32%), the III group-60–79 years, 11 patients (22%). All patients underwent hormonal (GH, IGF-1) studies.
Results
The levels of hormones of GH and IGF-1 remained high in the I group in 22% of patients, and in group III in 9%. Remissions reached 64% in the III age group. The highest level of GH content occurred in the age range from 45 to 59 years and was 77.5±9.68 mMe/l, and from 26 to 44years it was 68.1±6.84 mMe/l. After RT, this indicator in both age groups was almost equally suppressed, but not up to the norm. The decrease in the GH level to normal was observed in I age group in eight patients, and in the II age group in five patients it was 2.65±2.2 mMe/l and 2.23±1.4 mMe/l, respectively. In group III, in 11 patients before RT, the mean level of GH was 46.5±8.2 mMe/l. After RT, the level of GH decreased in this way: not suppressed only in one patient and was 22.1±0.89 mMe/l, in three patients the level of GH was suppressed, but not up to the norm and amounted to 6.7±0.7 mMe/l, only seven patients were suppressed and amounted to 2.46±2.2 mMe/l.
Conclusion
In all age periods, even in the period of the most activity pituitary adenoma-at the age of 26–44 years, RT is a rather effective method of treatment and gives positive results in most cases.

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AEP1087

Carotid ultrasound assessment in patients with acromegaly

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Objective
Acromegaly is characterized by chronic hypersecretion of growth hormone (GH) with increased concentration of IGF-1. It is known that patients with acromegaly have a high risk of developing cardiovascular diseases. We evaluated vascular changes by performing echodoppler ultrasonography in our series of patients.
Methods
Ultrasonographywas performed on 10 patients within one week after transsphenoidal surgery. The study includes 6 male and 4 female patients with an average age of 55.2 years. Intima-media thickness (IMT) of both internal carotid arteries was measured by M-Mode ultrasonography.
Results
Mean time between symptom onset and diagnosis was estimated as 10 years. All 6 male patients showed no structural arterial changes (6/10). Mild carotid wall plaques were detected in 3 female patients (3/10), the haemodynamic assessment was within normal range. One female patient showed severe vascular abnormalities (1/10).
Conclusion
In our series, all male patients showed normal findings in the echodoppler ultrasonography. Plaques could only be detected in female patients. The prevalence for severe atherosclerosis is 10%.

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AEP1088

Cushing's disease recurrence during peripartum period: A case report

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Introduction
Even with a high incidence of infertility owing to the suppressive effects of hypercortisolism in the gonadal axis, either associated or not to hyperandrogenism and ovulatory dysfunction, Cushing's syndrome (CS) during pregnancy has been reported. This could be due to a greater rate of CS among women in reproductive age; however, it is a rare condition, with fewer than 200 cases reported in the literature. In general, CS affects 2–25 people to every 1 000 000 per year. Although most cases during pregnancy are caused by autonomous cortisol secretion of adrenal glands, there are reports of Cushing's disease (CD) within this population, providing unfavorable mother-fetus outcomes. We present a case of spontaneous pregnancy in a patient in remission of CD, that recurred during peripartum period.
Case report
A 38-year-old patient presented to the endocrinology clinic with a recent diagnosis of type 2 diabetes mellitus and systemic arterial hypertension. After the initial workup, CD was diagnosed and promptly treated with transsphenoidal surgery. In the following years there was no sign of recurrence and, five years later, the patient became pregnant. In the first trimester of pregnancy, there was a worsening of blood glucose levels and insulin has been prescribed. The patient's condition did not improve and led to premature birth at 31 weeks of pregnancy. She remained with hyperglycemia, elevated blood pressure and asthenia, accompanied by flank purple striae, facial plethora and increased fat in the cervical area, up until two months post-partum. Laboratory workup after obstetric hospital discharge revealed increased late-night salivary cortisol of 9.71 ng/dl (0.8–1.2 ng/dl) and a 7.8% glycated hemoglobin. Plasma cortisol after 1 mg of dexamethasone was 12.2 mg/dl and ACTH 30.7 and 35 pg/ml. A new exam showed a pituitary microadenoma and the patient was again referred to the Neurosurgery service.
Conclusions
CS is a rare condition in pregnancy due to hypercortisolemia-induced infertility. Moreover, clinical features of CS can overlap physiological changes during the peripartum period; therefore, it is essential a high suspicion of recurrence in pregnant patients with a history of CS. Medical treatment is mandatory as deleterious peripartum outcomes may occur. Neurosurgery in the second trimester is the standard CD treatment in pregnancy. Cabergoline may be used, even though case reports with medical therapy alternatives are scarce. Our patient unfortunately had complications, without proper

treatment during pregnancy because of a low clinical suspicion by the obstetrics team.

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AEP1089

A homozygous hypomorphic BRCA2 variant in primary ovarian insufficiency without cancer or Fanconi anemia trait

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BRCA2, is a gene with a critical role in DNA repair and homologous recombination in somatic cells. Patients with *BRCA2* biallelic mutations develop Fanconi Anemia (FA), a severe life-threatening condition characterized by pancytopenia and multiple malformations and malignancies, while women with monoallelic alteration are at high risk to develop breast or ovarian cancer (up to 60%). Primary Ovarian insufficiency (POI) affects 1% of women under forty and is a public health problem. The genetic causes of POI are highly heterogeneous with isolated or syndromic forms. Recently, mutations in genes involved in DNA repair have been shown to cause POI. Here, using exome sequencing, we surprisingly uncovered a homozygous pathogenic variant of BRCA2 in a patient with isolated POI but without cancer or FA in all her family. The homozygous missense c.8524C>T/p.R2842C *BRCA2* variantchanges a strictly conserved residuelocated in BRCA2 DNA-binding domain. We demonstrated that this alteration only mildly altered the function of the protein usingseveral *in vitro* functional assays in primary and lymphoblastoid immortalized cells. Hence, the patient's cells showed intermediate levels of chromosomal breaks, cell proliferation and radiation-induced RAD51 foci formation compared to controls and FA cells. R2842C-BRCA2 only partially (~30%) complemented HR efficiency compared to WT-BRCA2. We show that BRCA2 is expressed in the fetal ovary in meiotic germinal cells which undergoing a high level of DNA breaks and subsequently repair. Our findings extend the phenotype of BRCA2 bi-allelic alterations to fully-isolated POI. This study has a major impact on the management of patients with POI and the genetic counsellingthat should now be addressed while keeping in mind a possible defect in a major DNA repair gene such as *BRCA2*.

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AEP1090

Climacteric symptoms and stress management techniques in peri- and early postmenopausal women

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Introduction
The hypothalamic-pituitary-ovarian and/or adrenal axis as well as the autonomous nervous system affect significantly the intensity of menopausal symptoms Pre-existing levels of stress may affect the individual perception of menopausal symptoms. We aimed to evaluate the efficacy of a structured stress management program to reduce levels of stress and severity of climacteric symptoms, in a sample of middle-aged Greek women.
Methods
The sample consisted of 61 women with varying severity of climacteric symptoms, aged 40 up to 65 years, retrieved from the Menopause clinic of Aretaieio Hospital, National and Kapodistrian University of Athens, Greece. Women were randomized into the intervention group ($N=31$) and the control group ($N=30$). An 8-week stress management program was offered to the intervention group, which included structured sessions on healthy eating, daily exercise as well as teaching of self-awareness cognitive restructuring and relaxation techniques. We evaluated the following parameters both at baseline and after the completion of the program: 1) Climacteric symptoms (Green Climacteric Scale – GCS), 2) Mood status (Depression Anxiety Stress Scale, DASS); 3) Sleep quality (Pittsburg Sleep Quality Index, PSQI); 4) Self-esteem (Rosenberg Self-esteem Scale); 5) Health locus of control (HLC). Associations were evaluated using repeated-measure mixed-model ANOVA.
Results
We found significant time × group interaction with regards to: i) GCS-Psychological symptoms ($F=144.727$; $P<0.001$); ii) GCS-Vasomotor symptoms ($F=62.917$; $P<0.001$); iii) GCS-Physical symptoms ($F=41.233$; $P<0.001$); iv) PSQI-Subjective sleep quality ($F=27.094$; $P<0.001$); v) PSQI-Sleep latency ($F=10.424$; $P=0.002$); vi) PSQI-Sleep disturbance ($F=24.186$; $P<0.001$); vii) PSQI-Daytime dysfunction ($F=10.668$; $P=0.002$); viii) DASS-Depression ($F=13.249$; $P=0.001$); ix) DASS-Stress ($F=9.546$; $P=0.003$). Scores of vasomotor symptom severity, anxiety and depression were significantly lower at follow-up compared with baseline values, only in the intervention group.
Conclusion
An alternative non-pharmacological approach to the management of climacteric symptoms. Climacteric symptoms may be effectively managed with education on stress management techniques.

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AEP1091

Low FT3 serum values are associated with markers of disease severity, evaluated during the acute phase of COVID-19

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Low T3 syndrome is a frequent finding in patients with critical illness, particularly in those admitted to intensive care units. It is generally considered an adaptive state of thyroid hormone (TH) economy, but many evidences indicate that it may represent a negative prognostic factor too. The prevalence and clinical relevance of the Low T3 syndrome in coronavirus infections has not been evaluated yet. We have measured thyroid hormone levels and analyzed anamnestic, epidemiological, clinical, biochemical and radiologic data of 62 patients affected by COVID-19 in search of possible correlation between all these parameters and the serum FT3 values. Patients were subdivided into two groups according to their serum FT3 levels, measured during the acute phase of the disease. Group A consists of 38 patients showing low levels of FT3 (<1.7 pg/ml) and Group B consists of 24 patients with normal levels of FT3 (>1.7 pg/ml and<3.71 pg/ml). We have measured several serum markers, radiologic and clinical scores of the severity of the disease and we have searched for a possible correlation between FT3 serum values and all these markers and scores. We observe a positive correlation with many disease severity markers and scores examined. The Absolute Neutrophil Count, the related NLR and dNLR ratios are higher in Group A, compared to Group B. Reduced FT3 serum values correlates with reduced total count of CD3+ lymphocytes and with reduction of both helper-inducer and suppressor-cytotoxic T cells. Low FT3 values correlate also with increased levels of inflammation, tissue damage and coagulation serum markers. Finally, low FT3 serum levels correlated with Sequential Organ Failure Assessment (SOFA) score, Lung Inflammation Prognostic Index (LIPI) and radiological Total Severity Score (TSS). Our study demonstrates that low levels of FT3, during the acute phase of COVID-19, are associated with biomarkers of tissue damage, inflammation, coagulation and with scores,

indexes of clinical and radiological severity of the disease. Low FT3 serum levels can be considered as a novel biomarker of the severity of the disease.

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AEP1092

Cholesterol and Graves' Orbitopathy (GO): 'A new decision-making algorithm based on baseline low density lipoprotein cholesterol (LDLc) and early GO clinical response to parenteral corticosteroids'

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Introduction
Parenteral corticosteroids (PC) are effective for the treatment of active moderate to severe (AMS) Graves'orbitopathy(GO). A correlation of GO activity with cholesterol has been described. No evidences are available about cholesterol levels and the clinical efficacy of PC in AMS-GO.
Aim
Was to detect the predictive role of cholesterol on medium term clinical outcome of PC therapy in AMS-GO.
Methods
We studied 87 patients treated with PC because of AMS-GO. GO evaluation was at baseline, 6 (W6) and 12 weeks (W12) after starting PC. Patients were Improved (I) or Not Improved (NI) by the EUGOGO overall clinical criteria (CI): I or NI W6CI or W12CI and by the Clinical Activity Score (CAS): I or NI W6CAS or W12CAS.
Statistic
By univariate and binary logistic regressions analysis setting W12CAS or W12CI categories as outcome variables; independent variables included LDL cholesterol (LDLc), W6CAS or W6CI categories. For the W12 outcome by CAS (W12CAS) regression model, the best cut-off was calculated by ROC curve analysis and by Youden's test.
Results
We retrospectively studied 22 males and 65 females, median age 45 years, who received a median PC cumulative dose of 52.3 g/kg body weight. Responders at W6 (early responders) showed a 13 times greater chance to be classified as improved at week 12 when compared to early not responders (OR 13.7 and 13.1, $P<0.001$). NI-W12CAS patients had a higher baseline LDLc cholesterol than I-W12CAS patients (mean rank 40.95 vs 30.49; $P=0.045$ respectively). The regression model built for W12CAS outcome was statistically significant, $\chi^2(2)=15.985$, $P<0.001$ and both W6CAS and LDLc resulted statistically significant predictor variables. By binary logistic regression results, we built a predictive model: $\frac{1}{1+e^{-(2.95-0.025x_1+2.57x_2)}}$, where x_1=LDLc (mg/dl); x_2=W6CAS outcome ($x_2=1$ for I_{W6CAS}; $x_2=0$ for NI_{W6CAS}). ROC analysis and Youden's test identified a predicted probability of improving at W12CAS=0.664 as best cut-off. A W6CAS and LDLc based decision-making algorithm was finally elaborated: LDLc>190 mg/dl suggests to treat hypercholesterolemia before to start PC therapy being too low the chances to reach a W12CAS improvement.
Conclusions:
Early clinical response to corticosteroids is determinant of the 12 weeks AMS-GO clinical outcome when evaluated both by CAS and CI. LDLc improves the predictivity of W12CAS final outcome, LDLc baseline levels>190 mg/dl reduce the chances of improving at 12W by CAS independently of early W6CAS response.

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AEP1093

Autoimmune thyroiditis has a protective role on papillary thyroid cancer: Insights from a new mouse model

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The relationship between papillary thyroid cancer (PTC) and autoimmune thyroiditis remains controversial. To gain mechanistic insights, we developed a mouse model by combining three strains: $BRAF^{V600E}$ knock-in and TPO-CRE-ER transgenic to induce PTC upon tamoxifen injection, and NOD.$H2^{h4}$ congenic to induce thyroiditis upon iodine administration.
A total of 113 mice of the desired genotype (BRAF mutant homozygous, CRE transgenic hemizygous on the NOD.$H2^{h4}$ background) were generated and separated into three cohorts. Mice in cohort 1 ($n=50$) were observed until death after tamoxifen and/or iodine treatment(s) to define the natural history of PTC and thyroiditis, while mice incohorts 2 and 3 ($n=63$) were sacrificed at a fixed time point after treatment (16 weeks after the first tamoxifen injection). Each cohort comprised six experimental groups: in Group 1 ($n=22$) tamoxifen and iodine were begun simultaneously, in Group 3 ($n=20$) tamoxifen followed iodine treatment, and in Group 5 ($n=23$) only tamoxifen was used. Each of these groups had its own control, (defined as group 2, 4, and 6 respectively) where no tamoxifen was given. In addition to survival, outcome measures included monthly assessment of thyroid ultrasound, thyroid function (TSH and T4), thyroglobulin and thyroperoxidase antibodies, and thyroid histopathology and flow cytometry at the time of sacrifice. In mice observed through their life time (cohort 1), tamoxifen induced the development of PTC in all three groups (1, 3, and 5) but with significantly different aggressiveness. While groups 1 and 5 died at 36 weeks of age, mice with preceding thyroiditis (group 3) died much later (after one year of age, $P<0.001$). In mice sacrificed at 16 weeks post tamoxifen, the incidence of PTC was significantly smaller in group 3 than groups 1 and 5 ($P<0.0001$), again indicating a 'beneficial' effect of pre-existing thyroiditis. Thyroglobulin antibodies developed, as expected, in mice treated with iodine and persisted throughout the observation time, but did not distinguish between the outcomes. On the contrary, thyroperoxidase antibodies developed later but remained elevated only in mice developing PTC. Lymphocytic infiltration in PTC lesions was greater in group 3 than group 1 ($P=0.002$) or 5 ($P=0.04$), and featured a unique expansion of CD8+ effector memory T cells ($P=0.009$). Overall, the study shows that pre-existing thyroiditis protects from PTC aggressiveness and progression, a protection that, however, disappears when thyroiditis and PTC are induced synchronously.

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AEP1094

Identification of thyroid disease in pregnant women varies by analytical method and type of thyroid function test

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Objective
Physiological alterations challenge the assessment of maternal thyroid function in pregnancy. It remains uncertain how the reference ranges vary by week of pregnancy, and how the classification of maternal thyroid disease vary by analytical method and type of thyroid function test.
Method
Consecutively collectedserum samples from 6.282 pregnant women in the North Denmark Region, 2011–2013, were used for the measurement of thyrotropin (TSH), total and free thyroxine (T4), total and free triiodothyronine (T3), and T-uptake using 'Method A' (Cobas 8000, Roche Diagnostics). TSH and free T4 were also previously measured using 'Method B' (ADVIA Centaur XP, Siemens Healthineers). Pregnancy week- and method-specific reference ranges (2.5 and 97.5 percentiles) were established after the exclusion of multiple births, women who were positive for thyroid peroxidase antibodies (TPO-Ab) and/or thyroglobulin antibodies (Tg-Ab), had thyroid or other autoimmune diseases or used thyroid interfering medication. Box-Cox transformation and Tukey's fences were used for detection and exclusion of outliers. The established reference ranges were used to classify maternal thyroid function, and classifications were compared

by analytical method and type of thyroid function test. Roche Diagnostics supported the study by offering a discount for the thyroid function tests performed.
Results
The reference ranges for TSH showed a gradual decrease during pregnancy week 4–14, a gradual increase was observed for total T4, total T3, and T-uptake, whereas free T4 and free T3 showed less variation. Altogether 689 of the pregnant women had TSH outside the reference range with either method A or B, and 541 of these (78.5%) had an abnormal TSH result with both methods. For free T4, 707 of the pregnant women had a test result outside the reference range with either method A or B, and 216 (30.6%) with both methods. When both TSH and free T4 were used for classification of maternal thyroid function, Method A classified 935 with abnormal thyroid function, Method B a total of 903, and the methods agreed on 554 individuals. When TSH and total T4 were used, 947 were classified with abnormal thyroid function, and classifications by TSH in combination with either total T4 or free T4 agreed on 584 individuals.
Conclusion
Even when pregnancy week- and method-specific reference ranges were established, the classification of maternal thyroid disease varied considerably by analytical method and across the different clinical available thyroid function tests. The findings raise a concern about misclassification, particularly for the use of free thyroid hormones.

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AEP1095

Low serum IL-17A in pregnancy during second trimester is associated with an increased risk of subclinical hypothyroidism

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Problem
Interleukin-17A (IL-17A) has a role in sustaining normal pregnancy. IL-17A is also associated with thyroid autoimmunity during pregnancy. This study sought to investigate whether IL-17A is a risk factor for thyroid dysfunction during pregnancyin women negative for thyroid autoantibodies.
Methods of study
The study comprised 216 pregnant women with negative thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) during the second trimester who provided bloodsamples for serum IL-17A, thyroid autoantibodies and thyroid function tests. To further evaluate the ratio of CD4+IL-17A+Th17 cells, we collected peripheral blood from 26 women with thyroid-stimulating hormone (TSH) levels ≤2.5 mIU/l and 26 pregnancy-week matchedwomen with TSH levels >2.5 mIU/l, along with samples from 20 women with TSH levels ≤4 mIU/l and 20 pregnancy-week matchedwomen with TSH levels>4 mIU/l.
Results
he serum IL-17A levels and ratios of CD4+IL-17A+ cells were significantly lower in women with TSH >2.5 mIU/l than in those with TSH≤2.5 mIU/l (both $P<0.01$). Similar lower differences were noted in women with TSH >4 mIU/l than in those with TSH≤4 mIU/l (both $P<0.01$). Moreover, serum TSH correlated negatively with IL-17A levels ($\beta=-0.195$, $P=0.004$), but positively with the week of gestation ($\beta=0.284$, $P<0.001$). Logistic regression indicated that a lower serum IL-17A level was a risk factor for TSH>2.5 mIU/l [OR=0.453 (0.298–0.689), $P=0.000$] and TSH>4.0 mIU/l [OR=0.588(0.385–0.899), $P=0.013$].
Conclusion
A low serum IL-17A level during the second trimester is associated with an increased risk ofTSH>2.5 mIU/l and subclinical hypothyroidism.

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AEP1096

Limited genetic overlap between Hashimoto´s thyroiditis and Graves´ disease in Swedish twins: A population-based study

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Background
Hashimoto´s thyroiditis (HT) and Graves´ disease (GD) are known co-aggregate in families, but the magnitude and nature of a shared etiology is unknown. The aim of this study was to estimate the shared genetic influence on these diseases. In addition, we sought to examine if the heritability of HT and GD differs between men and women.
Methods
We used national health registries to identify cases of HT and GD in a cohort of 110 814 Swedish twins. By comparing intra-class and cross-twin cross-trait concordance in dizygotic and monozygotic twins, we calculated heritability and the proportions thereof shared between the diseases. Univariate estimates of heritability were calculated separately by sex.
Results
The heritability for HT and GD was 65% (95% CI, 61–70%) and 63% (95% CI, 55–72%) respectively. The genetic correlation was 0.35 (95% CI, 0.20–0.50) and shared genetic effects accounted for 8% of the variance for both HT and GD. Univariate heritability was significantly higher in men than in women for HT (90% vs 60%, $P<0.001$) but not for GD (79% vs 63%, $P<0.085$).
Interpretation
HT and GD appear to be only modestly related diseases. Hence, the term 'autoimmune thyroid diseases', commonly used to cluster these disorders, has limited validity from an etiological perspective. Moreover, the mechanisms contributing to disease are partly different for the sexes, with genetic components more important in men than in women.

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AEP1097

Central hypothyroidism: Are patients undertreated?

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Introduction
Thyroid hormone (TH) replacement therapy in patients with central hypothyroidism (CHT) cannot be reliably guided by TSH levels. Guidelines suggest substitution doses between 1.2–1.6 µg/kg body weight, aiming for free thyroxine levels (fT4) prior to intake in the upper part of normal. However, variability in TH metabolism, concomitant treatments and inaccurate interpretation of TSH levels still puts patients with CHT at risk for inappropriate substitution as compared to patients with primary hypothyroidism (PHT).
Objective
To compare levothyroxine substitution doses between patients with CHT and PTH, and to explore Quality of Life (QoL) in both groups, using two questionnaires, the SF-36 health score and the thyroid specific ThyPRO score.
Methods
This is a monocentric, cross-sectional study, performed at the Ghent University Hospital (Belgium). During 12 months, we consecutively included 70 patients, 41 patients with CHT and 29 patients with PHT. At the time of inclusion, all patients had to have a stable dose of levothyroxine during the past six months and patients with PHT needed to be euthyroid (defined as a TSH level within the reference range, 0.2–4.5 mU/l). Patients with malabsorptive disorders, malignancies or conditions affecting TH metabolism or dosing were excluded. All data was retrieved from medical files, timing of blood sampling was not specifically instructed, questionnaires were self-administered.
Results
Patients from the CHT and PHT group were comparable regarding age and BMI. There were no significant differences between patients with CHT and PHT regarding absolute dose of levothyroxine (100 [93.75–125.00] vs 107.14 [81.25–132.14] µg/day, $P=0.942$) or dose relative to body weight (1.34 [1.16–1.55] vs 1.51 [1.14–1.73] µg/kg/day, $P=0.265$). Individual doses, however, varied substantially (0.71–2.44 in CHT and 0.48–2.56 µg/kg/day in PHT). Randomly sampled serum levels of fT4 and fT3 did not differ between the two groups ($P=0.269$ and $P=0.132$, respectively) and were in the midrange for both groups. We could not demonstrate differences between both groups regarding QoL questionnaires.
Conclusion
In our patients with CHT, median levothyroxine dose was within the suggested range and although numerically somewhat lower not significantly different from patients with PTH. We neither found differences in QoL between both groups. Interindividually, however, substitution doses varied substantially in both groups, so an individual appraisal of every patient is warranted rather than a one-size-fits-all approach.

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AEP1098

Rho-kinase (ROCK1 and ROCK2) gene polymorphisms in patients with Graves' disease

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Graves' disease (GD) is an autoimmune disease caused by autoantibodies binding to and activating the thyroid-stimulating hormone receptor (TSHR). Chronic stimulation of the TSHR results in a hyperactive thyroid gland and hyperthyroidism. The purpose of this study was to determine the association between Rho-kinase (*ROCK1* and *ROCK2*) gene polymorphisms and GD in a Turkish population. A total of 142 patients with HT and 163 healthy control subjects were included to this study. Genomic DNA was analyzed using the dynamic array system (Fluidigm, CA, USA). The Chi-square or Fisher's exact tests were used for calculation of the significance of differences in frequencies. Bonferroni correction for multiple testing was used for polymorphism studies, and $P<0.0083$ (0.05/6) was considered statistically significant. There were marked changes in TT genotype (0.0%, $P<0.0001$) and T allele (1.4%, $P<0.0001$) frequencies for the *ROCK1* gene rs35996865 polymorphism in GD group when compared to controls (TT 12.9%, T 14.4%). For *ROCK2* gene rs965665 polymorphism, CG genotype frequency (6.9%, $P=0.0034$) was markedly low among GD cases when compared to the controls (CG 20.0%). However, no associations were found with *ROCK1* rs73963110, *ROCK2* rs726843, *ROCK2* rs2290156, and *ROCK2* rs10178332 polymorphisms. This is the first study showing that *ROCK1* rs35996865 and *ROCK2* gene rs965665 polymorphisms were associated with GD in the Turkish population. This study was supported by a project (SBAG-213S021) from the TUBITAK, Turkey.

Table 1 The genotype and allele distrubition of *ROCK* gen polymorphism in Graves patients and control group.

Gen/SNP	Genotype/Allele	Control	*n**	Patient	*n**	*P*
ROCK1 rs73963110	TT/TC/CC T/C	159/3/0 321/3	162	126/4/0 256/4	130	0.7039 0.7057
ROCK1 rs35996865	GG/GT/TT G/T	117/4/18 238/40	139	105/3/0 213/3	108	**0.0005** **<0.0001**
ROCK2 *rs726843*	CC/CT/TT C/T	53/74/36 180/146	163	46/43/39 135/121	128	0.0960 0.6085
ROCK2 *rs2290156*	GG/GC/CC G/C	70/72/18 212/108	160	73/38/19 184/76	130	0.0226 0.2831
ROCK2 *rs965665*	CC/CG/GG C/G	120/32/8 272/48	160	105/9/17 219/43	131	**0.0007** 0.7248
ROCK2 *rs10178332*	TT/TG/GG T/G	119/36/8 274/52	163	122/15/5 259/25	142	0.0186 0.0114

Table 2 The genotype and allele distrubition of *ROCK1 rs35996865* polymorphism.

Genotype/ Allele	Control (*n*=139) *n* (%)	GD (*n*v108) *n* (%)	*P*	OR (95% CI)
G/G	117 (84.2)	105 (97.2)		
G/T	4 (2.9)	3 (2.8)	1.0000	0.8357 (0.1827–3.822)
T/T	18 (12.9)	0 (0.0)	<**0.0001**	0.0301 (0.0018–0.5060)
G	238 (85.6)	213 (98.6)		
T	40 (14.4)	3 (1.4)	<**0.0001**	0.0838 (0.0256–0.275)

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AEP1099

Data retrieval to provide thyroid hormone reference ranges and set-points upon individualized characteristics

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Clinicians recognize patients persistently experience residual symptoms of thyrotoxicosis or hypothyroidism etc. despite having achieved circulating levels of TSH and FT4 within the conventional normal ranges. In fact, many pathological conditions affect preferred TSH and FT4. In addition, evidences indicate that the laboratory-quoted normal thyroid hormones as well as TSH reference range could not be always appropriate for everyone in clinical practice. In neonates, infants, children, adolescents and elderly serum concentrations of the thyroid hormones show a clear age and sex dependency. Age- and sex-specific normal reference intervals are an important prerequisite for interpreting thyroid hormone measurement. A comprehensive literature search was performed on PubMed, UPTODATE, NCBI over publications within the last 3 decades. A total number of 43 references were retrieved based on search terms including thyroid hormone reference intervals, age; sex; and related TSH intervals, thyroid disorders and optimal TSH range. We extracted data about concentration of thyroid hormones in various pathological conditions. We extracted thyroid hormones data in various physiological conditions e.g. pregnancy, menopause etc. This data was inserted in a MS Excel file and subsequently implemented into MATLAB software as a matrix. A GUI was then developed based collected data matrix to calculate individualized thyroid hormone set points based on patient input parameters comprise age, sex and several routine pathological conditions e.g. hypothyroidism, total thyroidectomy. Both euthyroid set points of patients with primary hypothyroidism, total thyroidectomy, and lobectomy etc., can be straightforwardly derived from hormone calculator App using personal indications of each patient. It can be shown that every individual has a preferred personalized set point. This software provide the preferred set points to be rationally computed using our proposed algorithm implementable for computer-aided calculations. This could facilitate precise targeted dosing of patients in personalized medicine. The proposed GUI could provide intra-individual physiological optimal ranges compared to laboratory-quoted normal ranges and assist physicians making proper decisions.

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AEP1100

The impact of strain elastography and 4d doppler in improving the presurgical evaluation of thyroid nodules with intermediate cytology results

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Fine needle aspiration (FNA) is recommended for diagnosing thyroid nodules with suspicious ultrasound (US) features. Bethesda categories III and IV have conflicting management approaches: follow-up or thyroidectomy. This study aimed to evaluate a multimodal US assessment of the lesions in order to clarify the therapeutic strategy in intermediate cytology cases. 64 successive Bethesda III or IV cases were included. US evaluation consisted of greyscale US, qualitative strain elastography (SE) and three-dimensional (3D) Color-Doppler. A linear multifrequency probe and a linear volumetric probe (Hitachi Preirus Machine, Hitachi Inc. Japan) were used. The nodules were described usingconventional US criteria: taller-than-wide shape, marked hypoechogenicity, irregular borders, inhomogeneity, microcalcifications and the presence/absence of suspicious lymph nodes. Lesions presenting with increased stiffness on SE (scores 3 and 4) and moderate/intense perinodular vascularization were consideredto associate an increased risk of malignancy. Based on these criteria, lesions were classified as low, intermediate, or high risk. The outcomes were compared to the pathology report post-thyroidectomy. Thyroid cancer was identified in 25% (16 cases) and borderline follicular neoplasia was found in five cases. Given the recommendation of watchful waiting in this category, it was considered together with the malignant lesions, resulting in a number of 21 cancer cases. SE alone detected thyroid cancer with an accuracy of 82.81% (54/64 cases), a proportion of 80% of the nodules displaying score 4 and 66.6% of score 3 cases proved malignant. Most of the proven malignant nodules (15/21) showed important vascularization in the surrounding tissue. The prevalence of cancergrew with the degree of stiffness (9.0%–15.0%–66.6%–80.0%), but also with the intensification of vascular perinodular pattern (18.2%–

27.7%–35.29%–50.0%). The multimodal US evaluation of intermediate cytology cases, including B-mode, SE, and volumetric Doppler demonstrated a sensitivity of 85.7%, a specificity of 88.3%, and an accuracy of 90.3% in identifying thyroid malignancy. The detection ofhighly suspicious featuresusing qualitative SE, and 3D Doppler in addition to the conventional ones, did increase the risk of cancer.

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AEP1101

Measurement of calcitonin in nodular thyroid disease approach: The experience of a tertiary centre

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Introduction
It is universally accepted that calcitonin (CT), a hormone secreted by the parafollicular cells of the thyroid, is a specific, sensitive and early marker of Medullary Thyroid Carcinoma (CMT), with higher diagnostic accuracy than fine needle aspiration biopsy(FNAB). However, the routine measurement of serum CT during assessment of nodular thyroid disease (NTD) remains controversial due to rarity of this cancer and possible false positive results.
Aim
To evaluate the frequency of hypercalcitoninemia among patients with NTD,the prevalence of MTC in these cases and the concordance with cytologic results.
Methods
We present a retrospective study including patients with measurement of serum CT during investigation of NTD between january 2010 and june 2019. Data regarding cytologic results, performance of surgery and histological diagnosis were collected. Hypercalcitoninemia was established as a serum CT value >10 pg/ml. These patients were categorized, according the CT levels, in 2 groups: G1- serum CT 10–100 pg/ml; G2- serum CT ≥100 pg/ml. Patients with personal or familial history of MTC or MEN-2 were excluded.
Results
In a total of 1124 patients with serum CT levels measured during the study of NTD, 41 (3.6%) had hypercalcitoninemia [G1: 34 (3.0%); G2: 7 (0.6%)]. The FNAB was performed in 34 (82.9%) cases of high levels of CT [G1: 27 (79.4%); G2: 7 (100%)] and a cytologic result sugestive of MTC was found in 4 (11.8%) [G1: 1(3.7%); G2: 3 (42.9%)]. Among those with hypercalcitoninemia, 15 (36.6%) underwent to surgery [G1: 9 (26.5%); G2: 6 (85.7%)] and in 9 (60.0%) it was confirmed the histological diagnosis of MTC [G1: 3 (33.3%); G2: 6 (100%)]. Among these patients, beyond the 4 cases with FNAB compatible with MTC, 1 was submited to thyroidectomy due a MTC metastasis finding, and the remaining had the following cytological results: follicular neoplasm ($n=1$), suspicious of papilar carcinoma ($n=1$), suspicious of malignancy ($n=1$) and benign result ($n=1$). The histological diagnosis distribution of the remaining 6 operated patients was as follows: follicular carcinoma ($n=2$), follicular hyperplasia ($n=3$) and C cells hyperplasia ($n=1$) and all cases belonged to G1.
Conclusion
We documented a prevalence of hypercalcitoninemia in NTD of 3.6%, quite similar to data reported in literature. It has been described a MTC rate range from 0.3 to 1.4% in patients with NTD and from 10 to 40% in hypercalcitoninemia status, which is concordant with our results (0.8% and 22%, respectively). Despite the limited number of individuals, serum CT showed higher diagnostic accuracy to MTC than cytologic study and for values of CT ≥ 100 pg/ml, the positive predictive value was 100%.

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AEP1102

Microarray profile of B cells from Graves' disease patients reveals biomarkers of proliferation

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B lymphocytes are the source of autoantibodies against the thyroid-stimulating hormone receptor (TSHR) in Graves' disease (GD). Characterization of autoimmune B-cell expression profiles might enable a better understanding of GD pathogenesis. To reveal this, the expression levels of long noncoding RNAs (lncRNAs) and mRNAs (genes) in purified B cells from patients with newly diagnosed GD and healthy individuals were compared using microarrays, which elucidated 604 differentially expressed lncRNAs (DE-lncRNAs) and 410 differentially expressed genes (DEGs). GO and pathway analyses revealed that the DEGs are mainly involved in immune response. A protein–protein interaction network presented experimentally validated interactions among the DEGs. Two independent algorithms were used to identify the DE-lncRNAs that regulate the DEGs. Functional annotation of the deregulated lncRNA–mRNA pairs identified 14 pairs with mRNAs involved in cell proliferation. The lncRNAs TCONS_00022357-XLOC_010919 and n335641 were predicted to regulate TCL1 family AKT coactivator A (TCL1A), and the lncRNA n337845 was predicted to regulate SH2 domain containing 1A (SH2D1A). TCL1A and SH2D1A are highly involved in B-cell proliferation. The differential expression of both genes was validated by qRT-PCR. In conclusion, lncRNA and mRNA expression profiles of B cells from patients with GD indicated that the lncRNA–mRNA pairs n335641–TCL1A, TCONS_00022357-XLOC_010919–TCL1A, and n337845–SH2D1A may participate in GD pathogenesis by modulating B-cell proliferation and survival. Therefore, the identified lncRNA and mRNA may represent novel biomarkers and therapeutic targets for GD.

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AEP1103

Application of fuzzy logic controller to optimize thyroid hormone replacement therapy

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Conventionally, physicians adjust LT4 dose by clinical estimation based on their experiences and available guidelines; however, no computational algorithm exists to support their decisions. The objective of this study is to build an artificial decision support system utilizing fuzzy logic to propose a proper LT4 dosage regimen. We used THYROSIM software as the model of human thyroid hormone regulation to simulate a virtual thyroidectomized patient, setting the secretion rates of thyroid gland at 1%. A T-S fuzzy control algorithm was developed in MATLAB software to track TSH and T3 concentrations to their objective setpoints by adjusting LT4 dosage scheme. The result of our proposed LT4 dosage for the virtual patient was then compared with a conventional guideline implementing into THYROSIM software. The dosage of 165 µg LT4/day for our virtual patient results to 14 days lag time to achieve the objective setpoints of TSH and T3 while the proposed dosage by T-S fuzzy control algorithm could reach our objective in 8 days. Moreover, in contrast to fuzzy control system TSH concentraion in convetional therapy exceeded the upper bound limit for a priod of 7 days. Fuzzy logic could assist physicians by proposing a more proper LT4 dose scheme with an accuracy exceeding that of an expert provider. Therefore, a more proper treatment could be delivered by the clinicians using the decision tree of fuzzy logics.

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AEP1104

Hypothyroidism in utero suppresses pituitary-adrenal function in the ovine fetus near term: Implications for fetal maturation and the timing of birth

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Development of the fetal hypothalamic-pituitary-adrenal (HPA) axis is important for normal maturation of the fetus and the timing of parturition. In hypothyroid fetuses, gestational length may be prolonged and maturational processes delayed, although the role of the HPA axis is unknown. This study investigated the effects of hypothyroidism before birth on the structure and function of the anterior pituitary and adrenal glands in fetal sheep near term. All procedures were performed under the UK Animals (Scientific Procedures) Act 1986. In 15 twin-bearing pregnant ewes at 102–110 days of gestation (d; term ~145 d), one fetus was thyroidectomised (TX) while the other was sham-operated under general anaesthesia. At 143d, umbilical blood and fetal pituitary and adrenal glands were collected after euthanasia. Fractional volume and mass of adrenocorticotrophin (ACTH)-containing corticotrophs in the anterior pituitary gland were determined by immunohistochemistry and stereology. Adrenal zone composition, and adrenocortical and medullary mRNA abundances of key steroidogenic enzymes and growth factors, were determined by stereology and RT-qPCR, respectively. Data were assessed by Student's *t*-test ($P<0.05$). Plasma concentrations of thyroxine, triiodothyronine, ACTH and cortisol were lower in TX than sham fetuses. Fetal hypothyroidism increased absolute and relative (to fetal body weight) masses of the anterior pituitary gland (sham 22.0±1.5, TX 41.8±3.1 mg/kg) and corticotroph population (sham 6.8±0.4, TX 10.6±0.5 mg/kg).In the adrenal gland, absolute mass of the zona fasciculata was decreased (sham 117±12, TX 86±7 mg) and relative mass of the medulla was increased (sham 17.2±1.4, TX 22.4±0.8 mg/kg) by thyroid hormone deficiency, without any change in total adrenal mass. In TX fetuses, adrenocortical mRNA abundance was reduced by 42–63% for cholesterol transport protein StAR, steroidogenic enzymes CYP11A1, CYP17, 3β-hydroxysteroid dehydrogenase, CYP21 and CYP11B1, and for insulin-like growth factor-I (IGFI) and IGF type 1 receptor. Fetalhypothyroidism had no effect on adrenocortical ACTH receptor, IGFII or IGF type 2 receptor, or adrenomedullary phenylethanolamine-N-methyltransferase, IGFI, IGFII or IGF receptor mRNA abundance. Thyroid hormones are important regulators of the structure and secretory capacity of the pituitary-adrenal axis before birth. In hypothyroid fetuses, low plasma cortisol may result from impaired adrenocortical growth and steroidogenic enzyme expression, secondary to low circulating ACTH concentration. Greater pituitary corticotroph population during fetal hypothyroidism indicates compensatory cell proliferation and abnormal corticotroph capacity for ACTH synthesis and/or impaired hypothalamic input. Suppression of normal development of the fetal pituitary-adrenal axis by thyroid hormone deficiency may contribute to the delay in fetal maturation and delivery observed in hypothyroid offspring.

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AEP1105

MTHFR C677T polymorphism frequency and DNA methylation status in Georgian population with non-autoimmune hypothyroidism

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Introduction
Methylenetetrahydrofolate reductase (*MTHFR*) gene C677T polymorphism results in thermolabile, reduced functioning enzyme and predicts hyperhomocisteinemia and altered DNA methylation. On the other hand, several studies indicated a higher plasma homocysteine (Hcy) levels in patients with primary hypothyroidism than in healthy, euthyroid individuals, including some experimental studies that indicated decreased MTHFR activity in hypothyroid patients. We conducted this study to see whether there is an association between *MTHFR* C677T polymorphism, DNA methylation changes and non-autoimmune hypothyroidism (NAH) in Georgian population.
Materials and methods Study ethical approval was granted by Tbilisi State Medical University ethics committee. Informed written consent was obtained from all participants. Genomic DNA of 93 patients (mean age 51.3±15.17) and 96 healthy controls (mean age 51.6±16.65) were isolated using DNA blood Kit (Qiagen). Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis was used for genotyping *MTHFR* C677T. DNA samples underwent bisulfite modification (Qiagen) and methylation levels of Alu and LINE-1 were examined by the combined bisulfite restriction analysis-interspersed repetitive sequences (COBRA-IRS).
Results
The present study shows an association of *MTHFR* C677T polymorphism with NAH as T allele and CT genotype are more prevalent in patients then in control group (OR (CI) 3.75 (1.89 to 7.48), $P=0.0002$ and OR(CI) 5.03 (2.87 to 8.83), $P<0.0001$ respectively). On the other hand, our results suggest that hypermethylated loci (mCmC) at Alu elements are significantly lower (15%) in study group then in controls (37%) ($P<000.1$). As for LINE-1 the hypermethylated loci (mCmC) are also lower in study group (18%) then in controls (27%) ($P<000.1$).
Conclusion
The results of this case-control study suggest that the MTHFR C677T variant, was significantly associated with non-autoimmune hypothyroidism in Georgians. Also MTHFR 677TT genotype correlates with hypomethylation of Alu and LINE repetitive sequence in hypothyroid than in euthiroid individuals. All above indicates that C677T polymorphism may predispose development of non-autoimmune hypothyroidism.

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AEP1106

Dietary interventions for the treatment and management of autoimmune thyroid disease: A systematic review and meta-analysis

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Background
There is evidence that dietary interventions can reduce antibody levels in patients with autoimmune thyroid disease (ATD), which can have a beneficial effect on the clinical manifestations of the disease. The aim of this study was to review the literature regarding the different types of dietary supplementations and their effectiveness in the management of ATDs.
Methods
Using a predefined search strategy, four databases were searched (PubMed, Web of Science, CINAHL and Cochrane central register of clinical trials). Efficacy was assessed from randomized controlled trials and cluster randomized controlled trials including post-intervention mean, standard deviation and sample sizes for both the intervention and control group to calculate pooled effect sizes. Outcomes evaluated included serum levels of TSH, FT3 and FT4, levels of antibodies and change from baseline in symptoms of ATD. Risk of bias was assessed using the Cochrane tool for assessment of risk of bias.
Results
Twenty eight studies were included in the analyses, focusing on ATD ($n=9$), Graves' disease ($n=8$), Hashimoto thyroiditis ($n=7$), postpartum thyroiditis ($n=3$)and a prevention trial ($n=1$).Treatments included supplementation with Selenium ($n=15$), Vitamin C ($n=1$), Nigella sativa ($n=1$), a combination of carotene, vitamin C, Vitamin E and Selenium ($n=2$), Vitamin D ($n=4$), anatabine lozenges ($n=1$) and Myo-inositol plus L-selenomethionine ($n=1$).
Selenium supplementation improved serum TSH levels –0.48 (95% CI : –0.87 to –0.03); anti-TPO antibody –1.056 (–1.76 to –0.35); and FT4 levels –0.259 (95% CI : –0.57 to 0.05). Improvement across other outcomes was not significant. Nigella Sativa supplementation also showed an improvement in TSH –0.77 (95% CI : –1.41 to –0.13) and FT4 levels 0.67 (95% CI : 0.04 to 1.31). Myoinositol and selenium combination revealed improvement in FT4 0.54 (95% CI : 0.24 to 0.85) and Anti Tg antibody levels –0.52 (955 CI : –0.83 to –0.21). Iodine supplementation yielded a statistical significance only for anti TR antibodies –0.76 (95% CI : –0.96 to –0.56). Use of Vitamin A improved Anti Tg antibody levels 0.46 (95% CI : 0.13 to 0.79). Vitamin C and D supplementation revealed no significant effect on outcomes.
Conclusion
Dietary interventions were found to have a limited role in the management of ATDs. The evidence was generally of poor quality. We recommend that higher quality trials be conducted in the future to build a solid evidence base for use of supplements in autoimmune thyroid conditions.

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AEP1107

Prevalence of thyroid disease in end-stage renal disease patients

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Introduction
Chronic kidney disease is a rising cause of morbidity and mortality in developed countries, including end-stage renal disease (ESRD). Endocrine disorders are highly common endocrine complications among patients with chronic kidney disease, including those receiving dialysis. The prevalence of thyroid comorbidities in patients with chronic kidney disease is documented higher than in normal population.
Materials and methods
A cross-sectional observational single-center study was carried out in the Dialysis Center from May 2019- June 2019. One hundred twenty-three subjects were enrolled in this study. All patients were on chronic hemodialysis treatment with different primary causes of renal failure, with a mean duration of hemodialysis therapy 5.6±4.89 years. A complete clinical and biochemical profile was obtained for each patient. Conventional B-mode thyroid ultrasound was performed in all cases on Aixplorer Mach 30 (SuperSonic Imagine, France).The study aims to investigate the prevalence of morphological and functional thyroid disorders in patients with chronic kidney disease, with renal replacement therapy (hemodialysis).
Results
We evaluated 123 patients with end stage renal disease, with renal replacement therapy, with hemodialysis three times a week, mean age 62.2±11.01 years. The mean duration of hemodialysis therapy was 5.6±4.89 years. According to laboratory results we have found that 74.5% of patients from our study group were euthyroid, 24.4% percent were hypothyroid (16 females and 14 males),and 4 patients (3.3%) had subclinical hyperthyroidism. According to ultrasound results, 48.7% of patients have a normal thyroid appearance, 51.2% have a nodular goiter, defined as the presence of minimum one node in any thyroid lobe and 17.8% had autoimmune thyroiditis, with positive antibodies. The mean diameter of the nodules was 4.7±11.1 mm, the maximum size found on ultrasound was 24.6 mm and the minimum dimension was 2 mm. Thyroid disease was more prevalent among female patients, who present a 3.4 fold higher risk. We have also found that an increase of BMI with one unit raises the risk of developing thyroid disease with 1.083 times (P=0.018).
Conclusion
Chronic kidney disease and hemodialysis therapy have an impact on thyroid echo texture and morphology of thyroid gland. We have found that thyroid disease has a prevalence of 61.3% among patients with ESRD on hemodialysis, with a higher chance of developing thyroid disease for female gender, and the increase of body mass index raises the risk of developing thyroid disease by 1.083 times.

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AEP1108

Elastographic patterns in the evolution of Graves' disease: An observational study

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Introduction
The most common cause of hyperthytoidism is considered to be Graves disease (also known as Basedow disease), an autoimuune disorder. The most recent technique developed for measuring the tissue elasticity is considered to be sonographic elastography.
Aim
This study was conducted in order to determinate if any significant changes could be encountered in the elastographic patterns of the different evolutive stages of Graves' disease.
Material
We included in the study a total number of 24 randomized patients diagnosed with Graves disease, distributed in 3 categories: Onset (O), Stable (S) and Healed (H). In the Onset category were included 6 patients (with mean age 41.5±10.1), 10 patients (with mean age 43.5±12.1) were included in Stable category and 8 patients (with mean age 49.5±9.7) were in healed phase.
Method
All subjects were evaluated by all means: clinical, hormonal, immunological and convetional US. Strain elastography was performed with a HITACHI Preirus machine, with a 5–15 multifrequency linear probe. All the included patients underwent real-time strain elastography. The strain ratio was computed evaluating the strain of each lobe compared with sternocleidomastoid muscle on the same side.
Results
The strain ratios (SRs) (mean±standard deviation) of patients included in the cathegories O, S and H were 1.9±0.83; 1.3±0.46 respectively 0.7±0.17. Ranked in ascending order, SR values were: healed<stable<onset. Statistically significant (P<0.05) differences regarding thyroid stiffness were found between the groups.
Conclusion
The existence of various degrees of elasticity in the thyroid parenchyma depending of the evolutive phase was identified using real-time strain elastography.

Keywords: graves disease, elastography, thyroid, strain ratio.
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AEP1109

Thyroid imaging reporting and data systems (TI-RADS) and advanced ultrasound techniques: Compared stratification of the cancer risk

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The prevalence of thyroid nodules is increasing in the general population, thus detecting the ones at risk represents the main concern in clinical practice. The aim of the study was to compare four important Thyroid Imaging and Reporting Data Systems (TI-RADS) and assess how elastography and 4D Color Doppler vascularity evaluation improve the estimation of the malignancy risk. 133 nodules were evaluated by means of conventional ultrasound (US), elastography and 4D Doppler. All nodules were classified using the four selected systems and our proposed improved score: The American College of Radiology (ACR), the EU TI-RADS, Horvath TI-RADS and Russ' French TI-RADS. Outcomes were compared to the pathology exam. The percentage of malignancy was of 26.31%. The ACR and EU TI-RADS showed similar results: good sensitivity of 94.28% and 97.14%, NPV of 93.33% and 95.83%, but fairly poor specificity of 31.81% and 23.46%, a PPV of 35.48% and 31.19% respectively, with an accuracy of 42.8% and 45.8%. Horvath TI-RADS displayed better accuracy of 66.9%, slightly improved specificity (62.24%), but poorer sensitivity (80%). The French TI-RADS, whichadds elastography to the algorithm, showed better outcomes (Se: 91.42%, NPV:96.42%, Sp:82.65%, PPV:65.30%, and accuracy of 84.96%). A mean strain ratio (SR) value greater than 4 was found in 80% of malignant group and in only 12% of the benign nodules. The parameter itself showedgood correlation to the response variable: the pathology report (P<0.001). Similar accuracy was achieved when considering 4D vascularity as an additional parameter to the French score, butwhen studiedby itself, it proved beneficial for predicting cancer (P<0.001), thus it may bring important extra information in uncertain cases. Adding elastography and 4D vascularity information to the standard US evaluation of thyroid nodules did improve the estimation of the malignancy risk.

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AEP1110

The value of real-time strain elastography in the assessment of diffuse thyroid pathology

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Introduction
Autoimmune thyroid diseases are among of the most important causes of thyroid disfunction. Chronic Autoimmune Thyroiditis (CAT)and Graves' Disease (GD) are the major causes of hypothyroidism and hyperthyroidism, respectively.
Aim
The aim of this studywas to evaluate the efficiency of strain elastography in the differential diagnosis of Chronic Autoimmune Thyroiditis (CAT) and Graves' disease.
Material
In the study were included a total of 27 randomized patients with CAT (six males and 21 females withmean age 41.56±13.59), 12 patients with GD (three males and nine females with mean age 37.58±12.47) and 19 with normal-healthy thyroids (four males and 15 females with mean age 36.16±13.26).
Method: All 58 subjects underwent clinical examination, hormonal and immunological evaluation and conventional ultrasonography. For all the cases real-time strain elastography was performed by using HITACHI Preirus machine with a 5–15 multifrequency linear probe. The strain ratio was estimated by evaluating both thyroid lobes compared with sternocleidomastoid muscle on the same side.
Results
The strain ratios (SRs) (mean±standard deviation) of patients with CAT, GD and control group were 3.7±0.83; 2.15±0.28 and 0.87±0.2. Ranked in ascending order, SR values were: control group<Graves' disease<Chronic Autoimmune Thyroiditis. Statistically significant ($P<0.05$) differences regarding thyroid stiffness were found between the groups. The strain index ratio was higher both in CAT and GD than the control group.
Conclusion
Identifying different degrees of stiffness using strain elastography can help differential diagnosis of thyroid diffuse diseases.
Keywords: strain elastography, Graves disease, Chronic autoimmune tyroiditis, diffuse thyroid pathology, strain ratio.

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ePosters

Adrenal and Cardiovascular Endocrinology

EP1

Aldosterone to renin ratio and 24-h urine aldosterone level – suitability assessment in primary hyperaldosteronism prediction

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Introduction
Primary hyperaldosteronism (PHA) is the most common hormonal cause of hypertension concerning about 5–12% of hypertensive individuals. Aldosterone to renin ratio (ARR) and 24 h urine aldosterone concentration (24-UAC) are important tools in PHA screening diagnostics. The most appropriate cutt off values predicting PHA are still being discussed. The study is to assess siutability and to determine optimal cut off values of ARR and 24-UAC for accurate PHA prediction in uniform hypertensive population.
Methods
Fifty-nine hypertensive patients (age 49.20, s.d.: ± 14.45) with clinical suspicion of PHA, following a normal salty diet underwent 24 h-urine aldosterone concentration collection and ARR measurement after 2 h of verticalization. The verification of PHA diagnosis was based on the serum aldosterone concentration after the 0.9%NaCl loading test. Statistical analysis was performed. Evaluation of the test accuracy was performed based on the receiver operating characteristic (ROC) curve analysis.
Results
According to the salt loading test PHA was confirmed in 30 patients, and in 29 essential hypertension was diagnosed. The calculated sensitivity of ARR value >20, >30, >40 was respectively 100%, 92.59%, 85.19% for PHA prediction, while the specificity of ARR value >20, >30, >40 was respectively 44.44%, 66.67%, 74.07%. The calculated sensitivity of 24UAC >10, >12, >15, >17 μg/24 h for PHA prediction was respectively 73.91% 73.91% 68.18% 65.22% and the specificity was 69.23%, 76.92%, 85.71%, 92.31% respectively.
Conclusion
The results suggest that (1) the most appropriate ARR and 24-UAC cut off values consistent with the possibility of PHA confirmation are: ARR >40 and 24-UAC>15 μg/24 h in homogenous hypertensive population.

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EP2

Pregnancy during adjuvant mitotane therapy because of adrenocortical carcinoma – case report

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Introduction
Primary adrenocortical carcinoma (ACC) is a highly malignant but rare neoplasm. It can occur as a hormonally active or an inactive tumor. It is considered that about three-fourths of ACC cases are hormonally active, although they do not always give clinical symptoms. Mitotane (Lysodren) is registered by the FDA for the therapy of ACC, either for monotherapy or as a combined chemotherapy.
Case report
A 34-year-old woman, with a histopathological diagnosis of ACC (Weiss score 7 pts, Ki67-5%) after resection of the primary tumor in 2014, during the adjuvant mitotane therapy initiated in 2014 by an oncological center at the place of residence, was referred in 2017 to Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch because of the local recurrence of neoplasm with intraperitoneal dissemination. On the adimssion to our ward, the patient informed that she was pregnant. After the pregnancy was confirmed, the mitotane treatment was stopped (7 weeks' gestation). The MRI examination performed at 30 weeks' gestation revealed the progression of the disease. The patient gave birth to a healthy child in the 35 weeks' gestation (Apgar score 10/10). After the delivery the mitotane therapy was resumed and the EDP chemotherapy was performed.
Conclusion
Female patients with ACC during mitotane therapy are required to use effective contraception (mechanical preferentially). However, the mitotane belongs to the D category (embryotoxic) in the FDA Pregnancy Categories, no fetal complications were found in this case.

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EP3

Advantage and trustworthy of cortisol and dexamethasone evaluation in different biological matrices in patients with adrenal masses

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Biochemical function of adrenal masses is currently based on 1 mg post-overnight dexamethasone suppression test (pDST). Several approaches are recently developed, in order to reduce false positive/negative samples, only in retrospective series. They are based on the correlation of some different parameters, i.e. late-night salivary cortisol (LNSC) vs serum and salivary cortisol pDST; LNSC vs serum and salivary cortisol and serum dexamethasone pDST; LNSC and cortisone vs serum cortisol and salivary cortisol and cortisone pDST. Although these findings offer a better diagnostic performance, several conditions are still disappointed. No information is traceable about the harvest time of diurnal salivary and serum samples and no study include neither the levels of salivary nor urinary dexamethasone pDST. Aim of our study is to combine all these strategies in order to avoid the underestimated biases and obtain more precise information about the true "cortisol condition" of the patients.
To reach this purpose we assess both cortisol and dexamethasone concentrations in several samples: saliva at 2300 h before the drug administration, diurnal saliva and serum at 0800 h and also the urine collection from 2300 h to 0800 h. Analytes levels are measured using a validated liquid chromatography–tandem mass spectrometry method. In this study we included 20 subjects without morphological adrenal alteration (MRI assessment), dyslipidemia, hypertension and impaired glucose tolerance (healthy controls) and 50 patients with adrenal incidentaloma showing different cortisol levels ranging from normal to ACTH-independent hypercortisolism. In both series, LNSC were similar to salivary cortisol pDST, even if they were greater in the patients with adrenal incidentalomas and subclinical cortisol secretion. Serum dexamethasone levels were in reference ranges, while salivary and urinary dexamethasone found in these matrices require additional sample numbers in order to establish appropriate cut-offs. Our preliminary results suggest that the combination of these findings could represent an improvement to assess the individual cortisol status.

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EP4

Ectopic cushing syndrome: A cases-series in a tertiary centre in Spain

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Introduction
Ectopic Cushing Syndrome (ECS) is a rare disease associated with significant comorbidity. Among the causes of Cushing's syndrome (CS), ACTH-producing extrahypophyseal tumours are rarely reported. The aim of our study is to describe the clinical, diagnostic and therapeutic characteristics of patients with ECS treated in our Endocrinology department over a 15-year period.
Methods
A cross-sectional unicentric retrospective study was designed. Patients diagnosed of ECS in our hospital between 2005 and 2019 were included. Epidemiological, clinical, diagnostic, therapeutic and evolutive variables were recorded.
Results
A total of 7 patients (5 males and 2 females) with a mean age of 52 years (29–77 years) were included. The median time from the onset of symptoms to hypercortisolism diagnosis was two months. Most frequent comorbidities were hypertension in 6 patients (86%), and diabetes mellitus in 5 patients (71%). Cushingoid phenotype, oedema of limbs and proximal weakness was observed with 86%, 86% and 71% each. Regarding laboratory tests alterations, hypokalemic metabolic alkalosis, hypertransaminasemia (71%) and leucocytosis (57%) were detected. Relating to Cushing syndrome diagnosis, the mean serum cortisol was of 52.44 μg/dl (20–98), urinary free cortisol

2624.28 μg/24 h (838–6246) and ACTH 193.7 pg/ml (75–271). The ectopic origin was confirmed whether by dynamic tests in a total of 5 patients (CRH stimulation test and/or inferior petrosal sinus sampling) and/or by radiological images in 7 patients (CT, MRI, Octreoscan, FDG-PET/CT and/or 68Ga-DOTANOC PET/CT). The responsible neoplasm could be identified by histology in 6 out of 7 cases. They were mostly pulmonary neuroendocrine tumours (4 carcinoids and 2 small cell carcinoma (SCLC), and 3 of them presented metastatic dissemination at diagnosis. Regarding therapeutic management of CS, ketoconazole and metyrapone were indicated in 6 and 3 respectively. The treatment of the primary tumour included surgery in two cases, surgery combined with systemic therapy (chemotherapy and somatostatin analogues) in one case, sunitinib and somatostatin analogues in other case and chemotherapy-only in two patients. At follow-up 3 have died and 4 remain alive (3 free of disease and one with stable disease).
Conclusions
ECS is associated with significant morbidity and mortality both due to the complications derived from excess cortisol production and the tumour itself and its dissemination. Mortality differs according to the underlying primary tumour, showing SCLC the poorest prognosis. This fact highlights the importance of both hypercortisolism control and the antitumor treatment, which requires a multidisciplinary management.

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EP5

The effectiveness of treatment for primary aldosteronism in Iceland 2007–2016

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Introduction
Primary aldosteronism (PA) is a potentially curable cause of hypertension. In 2007, a standardized PA work-up protocol was introduced in Landspitali University Hospital (LUH), a tertiary care center for Iceland. The aim of this study is to review treatment response for patients diagnosed with unilateral and bilateral PA in LUH 2007–2016.
Methods
All charts for PA-patients aged ≥18, diagnosed 2007–2016 in LUH, were retrospectively reviewed. Saline infusion test confirmed diagnosis. Adrenal venous sampling distinguished unilateral (UD) from bilateral disease (BD). Adrenalectomy was offered for UD, otherwise patients were treated with aldosterone antagonists. Yearly follow-up consisted of monitoring blood pressure, serum-potassium and need for hypertension medication (HTM) and potassium supplementation (PS). Wilcoxon rank-sum test was used for comparison.
Results
Sixty-seven patients were diagnosed with PA during the study period; 40 BD and 27 UD. For BD, median systolic blood pressure (mSBP) at diagnosis was 160 (119–204) mmHg compared to 142 (115–189) mmHg at 1-year follow-up, $P=0.0032$. At 5-years, mSBP was 145 (121–168) mmHg, lower than at diagnosis ($P=0.012$). For UD, mSBP at diagnosis was 167 (104–214) mmHg compared to 141 (111–188) mmHg at 1-year, $P=0.0004$. For UD mSBP at 5-years follow-up was 134 (117–184), lower than at diagnosis, $P=0.0005$. Median diastolic blood pressure (mDBP) at diagnosis was 91 (64–132) mmHg for BD compared to 85 (41–106) at 1-year follow-up, $P=0.0092$. At 5-years, BD mDBP was 89 (65–100) mmHg, $P=0.15$ when compared to same group at diagnosis. For UD, mDBP at diagnosis was 102 (57–140) mmHg. At 1-year, UD mDBP was 90 (69–107) mmHg, lower than at diagnosis ($P=0.0076$). At 5-years, UD mDBP was 88 (69–100) mmHg, lower than at diagnosis, $P=0.011$. Median number of HTM at diagnosis was 3 (1–6) BD and 3 (0–5) UD. At 1-year, median HTM number was 3 (1–5) BD and 2 (0–5) UD. At 5-years, median HTM number was 2 (1–5) BD and 2 (0–6) UD. At diagnosis, 15 BD patients and 13 UD needed PS. Two from each group needed PS at 5-years.
Conclusions
In this nationwide study, we found that approximately 40% of the patients had UD. With specialised treatment, SBP and DBP reduced significantly in both subgroups. The results indicate that during the study period, only the most serious cases of PA were diagnosed as 42% of the patients in this study needed PS at baseline. The study emphasizes the importance of screening for PA in patients in Iceland.

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EP6

References values for midnight serum cortisol

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The loss of nychthemeral rhythm is a feature of endogenous hypercorticism that may be investigated by the assay of midnight salivary cortisol ($_{ser}$C0h) although often replaced by serum cortisol assay. However, manufacturers of cortisol immunoassays kits seldom provide reference values for this horary. We present here tentative reference values of $_{ser}$C0h with an automated imunoanalyzer (DXi800, Beckman Coulter).
The population retrospectively studied (2014–2017) consisted of in-patients mainly investigated for diabetes, hypertension, and obesity (214F/121M, 57 [25–75] years, BMI 27.5 [20.2–41.2], median [5th–95th] percentile). The patients that elicited the strongest clinical suspicion of hypercorticism were subjected to urinary sampling for cortisol assay and/or low dose dexamethasone supressing test.
$_{ser}$C0h ($n=415$) was 93 [36–251] nmol/l with a non-gaussian distribution in subjects with no confirmed hypercorticism. The upper reference limit (URL) of $_{ser}$F0 was 284 nmol/l (CLSI C28-A3 non-parametric method). Urinary free cortisol (UFC) was 17 [5–55] μg/d (ref 10–60 μg/d) Serum cortisol at 8 h ($_{ser}$C8h) was 336 [189–623] nmol/l (DXi800 reference values 185–624 nmol/l). There was no significant correlation of $_{ser}$C0h with BMI or UFC or $_{ser}$C8h.
The 10 subjects exhibiting $_{ser}$C0h>URL were diagnosed: metastatic cancer (3), pheochromocytoma (1), acromegaly (1), diabetes/alcoholism (1), stress (1), pseudoCushing syndrome (1) and adrenal incidentaloma (2). The stressed patient had normal UFC and low-dose DXM test (LDDT) 6 months later, the patient with pseudoCushing syndrome has the same status 3 years later. One patient with incidentaloma had normal UFC and LDDT 1 year later, and was later diagnosed multiple sclerosis. The other patient with incidentaloma had normal LDDT; adrenalectomy was requested because the tumour (30 mm) was heterogeneous with calcification but the patient was lost on follow-up.
We propose to use 284 nmol/l as URL for $_{ser}$C0h using the DXi800 cortisol assay. Prospective studies are pending to provide clinical specificities and sensitivities at this level. Comparisons with other immunoassays are also needed.

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EP7

Case report: Ectopic Cushing syndrome as paraneoplastic manifestation of an advanced small cell lung cancer

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Background
Ectopic Cushing Syndrom (ECS) represents approximately 12% of all patients with Cushing´s disease. Either ACTH (5–10%), CRH or cortisol is produced uncontrolled from nonpituitary tissue. Half of ECS cases are neuroendocrine lung tumors [carcinoid tumors>small cell lung carcinoma (SCLC)], but ECS is clinically apparent only in 1–5% of SCLC cases. Clinical features vary according to extent and duration of exposure to ACTH/Cortisol excess and include rounded erythematous face, acne, purple striae, proximal muscle wasting, edema, hypertension and metabolic alkalosis with hypokalemia. If possible, radical tumor excision is the treatment of choice. Ketoconazole, metyrapone, etomidate, mitotane, and mifepristrone and octreotied are second line options whereas bilateral adrenalectomy is the ultima ratio in case of pharmacological failure. Patients with ECS due to SCLC usually present at an advanced stage.
Case report
A 67-year-old male patient (BMI 26.5 kg/m²) with deterioration of known hypertension, diabetes mellitus on oral treatment (metformin/empagliflozin/

saxagliptin) and psoriasis but also hyperhidrosis, bruising, dizziness. Smoking history of 40 pack years. Severe hypokalemia with 2.17 mmol/l (3.3–4.5) and hyperglycaemia (plasma glucose: 20.3 mmol/l; HbA1c: 9.0%;) resulted from corticotropic excess [serum cortisol in nmol/l (101–536): max. 2710; profile: 2033 (0600 h) – 1266 (2400 h) – 1158 (1800 h) – 922 (1200 h); ACTH 339.8 pg/ml (4.7–48.8)]. No increase of ACTH seen in the CRH-test (−15 min: 350.0 – 0‘: 339.7 - … - 120‘ 345.9). Computed tomography (CT) scanning identified tumor lesions of the right lung, liver and bilateral adrenal glands. Liver biopsy provided histologic diagnosis for liver metastasis of a low differentiated, high proliferative SCLC (cT1bN3M1c, G3, extensive disease; MNF116 positive, AE1/AE3 positive, synaptophysin positive, CD56 positive, TTF-1 positive, KI-67-index 90%). Serum NSE was elevated: 51.5 ng/ml (0–12.5). Bradycard episodes (heart rate 35/min) due to reduced potassium levels were seen and cardiovascular surveillance and compensation of electrolyte imbalance at ICU was necessary. Cortisol excess led to susceptibility for infections and soor-esophagitis and aspergillosis of the lungs occured. Adrenostatic therapy with metyrapone (3500 mg/day) was started and serum cortisol normalized to 424 nmol/l. According to tumor board recommendation palliative systemic chemotherapy with etoposid and carboplatin was commenced. Dismissal from hospital was possible after 49 days and after 2 chemotherapy regimes. Medication at dismissal: metyrapone 3000 mg/day, spironolactone 200 mg/day, insulin therapy. Continuation of chemotherapy is planned.

Conclusions

Severe hypokalemia and cortisol excess in combination with brief disease duration should be suspected for ECS. Interdisciplinary therapy by endocrinologists, intensive care unit and oncologists is needed. Severity of hypercortisolism and tumor histology affect mortality and morbidity.

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EP8

Secondary hypertension due to middle-aortic syndrome in a young adult patient

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Introduction

Hypertension is a severe medical condition that significantly increases mortality and disability worldwide. Most hypertensive patients are classified with essential hypertension; however, secondary hypertension is present 5–10% of all cases. Aortic stenosis is a significant cause of secondary hypertension in children and adolescents. Middle-aortic syndrome constitutes 0.5%–2% of all cases of aortic stenosis. The stenosis involves the abdominal aorta and/or distal descending thoracic aorta and can include the renal and visceral branches.

Objective

We report a case of middle-aortic syndrome in a young adult with severe hypertension.

Results

The 21-year-old female patient was referred to our tertiary referral endocrine centre with resistant hypertension diagnosed at the age of 18 years. Her blood pressure exceeded normal ranges despite a triple combination of antihypertensive drugs (ACE inhibitor, calcium channel blocker and diuretics). Physical examination revealed equally elevated blood pressure on both arms (180/100 mmHg) and significantly lower blood pressure values on both legs (150/80 mmHg). According to the 24-h blood pressure monitoring, median blood pressure was 155/80 mmHg (day time median: 137/67 mmHg, maximum systolic blood pressure 220 mmHg; night time median: 164/86 mmHg, maximum systolic blood pressure 175 mmHg). Hormonal investigations were performed after optimising antihypertensive treatment not affecting the renin–angiotensin–aldosterone system. The laboratory investigations confirmed hyperreninemic hyperaldosteronism: supine aldosterone level was 17.2 ng/dl (reference range: 0.7–15.0 ng/dl), plasma renin activity was 4.41 ng/ml per h (reference range: 0.20–2.80 ng/ml per hour). The patient was euthyroid and eucortisolemic. Both kidneys showed normal parenchymal function and ultrasound morphology. Abdominal and thoracic computed tomography–angiography revealed significant stenosis of thoracic aorta at the segment of the X–XI thoracic vertebrae. Percutaneous transluminal balloon angioplasty and stenting was performed with success as her blood pressure normalised after the intervention. Long – term blood pressure control could be achieved with low-dose doxazosin monotherapy.

Conclusion

Our case highlights that secondary hypertension should always be considered in young patients with hypertension. Middle-aortic syndrome is associated with high morbidity and mortality due to the increased risk of cardiovascular disorders. As conservative drug treatment is rarely effective vascular intervention is required to normalize blood pressure and prevent end-organ damage.

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EP9

Which of the anthropometric indicators is the most useful tool in the assessement of potential inflammation in patients with non-functioning adrenal incidentalomas

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Introduction

Chronic inflammation is an important factor in type 2 diabetes and cardiovascular diseases development. Studies demonstrate that body fat, estimated by anthropometric indicators, correlates with inflammation indicators in chronic diseases. Ipso facto, it seems reasonable to suppose, that there would also be a correlation between anthropometric parameters and both, old and new inflammation indicators in patients with non-functioning adrenal incidentalomas.

Aim

The aim of the study was to evaluate anthropometric parameters and indicators – waist circumference (WC), BMI, WHR, WHtR, BAI, VAI, LAP, BRI, ABSI, RFM and its relationship with inflammation indicators – old one: insulin, CRP and new one: PLR (*platelet–lymphocyte ratio*), MPVLR (*MPV-to-lymphocyte ratio*), SII (*systemic immune–inflammation index*) in group of patients with non-functioning adrenal incidentalomas.

Material and methods

The study included 182 patients with non-functioning adrenal incidentalomas hospitalized in Endocrinology City Hospital in Piekary in 2014–2018. The exclusion criteria were mainly: other adrenal disorders, decompensated diabetes defined as HBA1 C% >7, kidney failure as eGFR<60 ml/min per 1.73 m^2, liver failure as bilirubin>2 mg/dl, INR>1.5 and albumins<3.5 g/dl, severe inflammation, treated cancer disease. Biochemical parameters (taken from the patient’s medical record) and anthropometric measurements were used to calculate anthropometric indicators. Patients were also analyzed with electrical bioimpedance to estimate percentage of body fat and visceral fat rate.

Results

The average age in studied group was 63 years, cortisol concentration at 0800 h was 12.05 μg/dl, CRP was 3.7 mg/l, insulin 12.8 μU/ml. There strongest correlation (P<0.05) was observed between insulin and: BRI (r=0.58), WHtR (r=0.58), BMI (r=0.58), RFM (r=−0.58). VAI correlated negatively (P<0.05) with MPVLR (r=−0.25) and PLR (r=−0.17), BAI with SII(r=−0.2). There was a positive correlation between CRP and BRI (r=0.16) as well as WC (r=0.16).

Conclusion

New anthropometric indicators, especially VAI and BRI, are more useful in the assessment of potential inflammation in studied group of patients with non-functioning adrenal incidentalomas, than the previous ones.

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EP10

Malignant neuroblastoma mimicking a metastatic paraganglioma – case report

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Background
Neuroblastomas are malignant tumors that arise from sympathetic plexus or adrenal medulla. Their clinical behavior can range from spontaneous regression to aggressive disease. Like paragangliomas, they have the capacity to secrete catecholamines and to express somatostatin receptors, which is important for diagnostic and treatment purposes. However, the differential diagnosis with paraganglioma can be challenging. We present a case of a catecholamine-producing tumor whose final diagnosis was not straightforward.
Clinical case
A 24 years female presented with dorsal, lumbar and pelvic pain, pelvic paresthesia, dysuria and fever in the last 2 months. The complementary exams showed elevated inflammatory parameters, normocytic normochromic anemia and a right pleural effusion. Antibiotic therapy and several exams were performed.
The computerized tomography scan (CT) revealed several soft tissue lesions (the 2 dominant ones located in left paravertebral areas): D3-D6 measuring 48×44×32 mm and D8-12 with 46×40×46 mm, sacred vertebrae (S1−S4) and iliac bones. The magnetic resonance confirmed well defined lesions and hyperintense in T2. A CT-guided biopsy of both dominant lesions was made, suggesting a paraganglioma positive for S-100, chromogranin and synaptophysin in immunohistochemistry in the superior lesion (D3-D6) and a schwannoma in the inferior (D8-12). No immediate complications of the procedure occurred. At that point she was referenced to our endocrine oncology center. It was required a positron-emission tomography (PET) with 68Ga-dotanoc, which showed hyperexpression of somatostatin receptors in the paravertebral lesions (SUVmax 5.2 in the superior lesion and 12.8 in the inferior), in the sacrum (SUVmax 6.3), in the fourth left rib (SUVmax 4.8) and right scapula (SUVmax 7.5). The total urine metanephrines were high (38.4 mg/24 h, normal range (NR)<1) and also the vanillylmandelic acid (86.6 mg/24 h, NR<14) and chromogranin A (546 ng/ml, NR<100). She started phenoxybenzamine and palliative treatment. A PET-18Fluorodeoxyglucose was performed showing extensive metastasis in bones, muscles and lymph nodes. At that time a review of the previous histology was made: it was diagnosed a poorly differentiated neuroblastoma and a ganglioneuroma in the superior and inferior paravertebral lesion, respectively. An osteomedullary biopsy was than performed and revealed neuroblastoma infiltration in the medulla. She started chemotherapy with vincristine, etoposide and carboplatin. During chemotherapy she developed dural metastases and she is being treated with cranial radiotherapy at this point.
Conclusion
This case illustrates the importance of considering the neuroblastoma in the diagnostic workup of apparently metastatic paraganglioma in young adults, even when catecholamines are produced, 68Ga-dotanoc uptake is present and immunohistochemistry profile is compatible.

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EP11

A case of coexisting carotid body paraganglioma, adrenal incidentaloma and malignant peripheral nerve sheath tumor. Coincidence or something more?

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Introduction
Paraganglioma (PGL) is a neuroendocrine tumor (NET) originating from the neural crest cells. Head and neck paraganglioma (HNPGL) often presents as an asymptomatic slow growing tumor and is rarely functional. Adrenal incidentaloma (AI) is defined as a silent adrenal mass detected on imaging performed for unrelated disorder. Malignant peripheral nerve sheath tumor (MPNST) is a variety of soft tissue sarcoma derived from cells of neural crest.
Case report
A 41-year-old normotensive woman with severe obesity is admitted to our endocrinology department after surgical intervention followed by radiotherapy for MPNST. Post-therapeutic follow-up MRI revealed a tumoral mass localised at the bifurcation of the right carotid artery with salt and pepper appearance, splaying of the internal and external carotid artery with approximately 31/27/35 cm. The patient underwent surgery and the immunohistological result showed typical Zellballen pattern, positive for synaptophysin, chromogranin, S100, and Ki-67 index was 5% which confirmed the diagnosis of carotid body paraganglioma. The surgical margins of resection were positive, therefore the patient was submitted to radiotherapy. In addition, a CT scan of the abdomen revealed a left adrenal gland hipodense lession with a density between −30 and −50 HU with approximately 25/20/18 mm, aspect suggestive of adrenal myelolipoma. Biochemical evaluation revealed diabetes mellitus type 2. Hormonal assessment showed slightly raised urinary metanephrines levels 387.5 (25–312 µg/24 h), normal values of NET associated markers and corticotropic axis. In order to investigate the possible existence of MEN2A syndrome we also measured calcitonin and PTH both within normal range.
Discussion
Since around half of HNPGLs are hereditary with SDH family gene (SDHx) mutations being responsible for the majority of cases, genetic testing is required. The particularity of the presented case is the association between PGL and MPNST both arising from neural crest derived cells, and AI which is found in approximately one fourth of patients with hereditary paraganglioma–phaeochromocytoma syndromes. Further studies are necessary in order to asses if there is an association between SDHx mutations and MPNST susceptibility.
Key words: head and neck paraganglioma, adrenal incidentaloma, malignant peripheral nerve sheath tumor

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EP12

Altered bone mass and microarchitecture in catecholamine-secreting malignant paraganglioma

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Introduction
Pheochromocytoma and most abdominal paraganglioma (PPGL) can secrete catecholamines. *In vitro* and *in vivo*, catecholamines modulate bone remodeling by stimulating bone resorption. In patients with PPGL, four studies have previously demonstrated an increase of biological markers of bone resorption, a decreased of bone density and a higher prevalence of vertebral fractures. We report two patients with malignant abdominal secreting paraganglioma presenting with osteoporosis and altered bone microarchitecture.
Case reports
Patient 1, 43 years-old, was operated for a norepinephrine-producing SDHB abdominal paraganglioma causing malignant hypertension. One year after surgery, magnetic resonance imaging (MRI) diagnosed metastases in T7 and L1 with concordant high uptake in 123I-MIBG and ^{18}F-FDG PET/CT imaging and additional multiple osteoporotic painful vertebral fractures outside the metastatic sites. A dual energy X ray absorptiometry (DEXA) showed lumbar (*T*score = −2.90) and left hip (*T*score = −2.70) osteoporosis. Patient 2, 35 years-old, had a norepinephrine and dopamine-producing SDHA paraganglioma with regional lymph nodes and liver metastases. DEXA revealed lumbar (*T*score = −3.10) and left hip (*T*score = −2.40) osteoporosis. A treatment by temozolomide and capecitabine was initiated. To evaluate bone structure, the patient underwent a high-resolution peripheral computed tomography (HR-pQCT) showing a moderate alteration of bone microarchitecture. At the right tibia, total density (Dtot) was measured at 275 mg HA/cm [normal for the age and the sex (*n*): 338 ± 51], trabecular bone density (Dtrab) at 173.3 (*n*: 199 ± 39), trabecular number (Tb.N) at 1.67 l/mm (*n*: 1.90 ± 0.33), trabecular thickness (Tb.Th) at 0.087 (0.09 ± 0.01). At the left radius, Dtot was measured at 311.4 mg HA/cm (346 ± 57), Dtrab at 179.9 (201 ± 35), Tb.N at 2 l/mm (1.97 ± 0.22), Tb.Th at 0.075 (0.09 ± 0.01). Catecholamine secretion was respectively 12-fold and 29-fold the normal values in these patients who had no other risk factors for osteoporosis than prolonged exposure to catecholamines.
Conclusion
Catecholamine excess can lead to secondary osteoporosis in secreting PPGL. We show here for the first time by the gold standard method, the HR-pQCT, an altered bone microarchitecture. Being aware of such complications is particularly important in malignant PPGL that may have progressive disease and higher catecholamine production contributing to more serious bone complications. Eventually, with bone metastasis present in approximately 70% of metastatic patients, the catecholamine-induced bone fragility can lead to fracture, pain and decreased quality of life as illustrated here.

We also believe that osteoporosis should be sought in every patient with malignant PPGL.

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EP13

Distinct clinical course of neuroendocrine tumors presenting ectopic ACTH tissue expression and secretion

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Two female patients, A – 61-year-old, B – 68-year-old, were admitted to hospital with symptoms of hypercortisolemia. Both of them were diagnosed with neuroendocrine tumor (NET), patient A with pancreatic NET G3 (Ki67 – 30%), and patient B with a disease with a probable primary origin in lungs - NET G2 (Ki67 - 15%). Both women had metastases to the liver. While laboratory results were similar in both cases (high level of cortisol – up to 1750 nmol/l and 1459 nmol/l (normal value: <497 nmol/l), ACTH – up to 184.40 pg/ml and 214.90 pg/ml (normal value: <63.30 pg/ml), hypokalemia, hyperglycemia, high BP), the clinical manifestation of the disease was quite different. Examination of patient A revealed signs of hirsutism, muscular atrophy, edema of the lower limbs, easy bruising. Patient B presented psychotic symptoms, such as delusions, aggressive and inadequate behavior, confusion. MRI scan of the pituitary gland in both cases revealed no tumor. In both patients, their liver biopsy samples from metastatic foci were tested for the ACTH expression and were positive. Patient A underwent left adrenalectomy, while resection of the right adrenal gland was impossible because of the tumor infiltration. The pathomorphological examination of the removed tissues revealed lipid-poor adenoma. Patient B did not agree for surgery. In both cases, metyrapone was administered as a treatment for Cushing syndrome. Due to the limited access to the drug and its temporary withdrawal, in both patients, cortisol level fluctuations accompanied by a transient aggravation of the general condition were observed. Patient A was treated with octreotide, as well as capecitabine and temozolomide (CAPTEM) and patient B was qualified for treatment with everolimus due to lack of somatostatin receptor expression in HYNIC-TOC. Patient B died 6 months after the diagnosis, while patient A achieved partial remission of the disease and her general condition improved. Ectopic adrenocorticotropic hormone (ACTH) secretion (EAS) may be a form of ACTH-dependent Cushing syndrome in patients diagnosed with neuroendocrine tumors. The treatment of underlying disease together with the treatment of hypercortisolemia should be considered and may constitute a challenge. Metopirone might be a useful drug to reduce concentration of cortisol. However, adrenalectomy may remain basis for the treatment of EAS affecting patient's quality of life and prognosis. The assessment of ACTH expression in the neuroendocrine tumor metastases may guide the management of patients diagnosed with Cushing syndrome due to EAS.

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EP14

Descriptive analysis of suprarrenal carcinoma in our center. Clinical characteristics and evolution

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Introduction
Adrenocortical carcinoma (ACC) is a very rare entity with a variable clinical presentation.
Objective
To review the casuistry of ACC in our center in the last 15 years and to assess clinical characteristics and evolution in our patients.
Material and method
We searched cases of ACC from 2004 to December 2018 registered in the Pathology Department.
Results
Fifteen cases were found, 9 women and 6 men. The mean age at diagnosis was 49.6±12.7 years (range 27–82 years). The initial symptom was local discomfort (5), clinical hypercortisolism (4) constitutional syndrome (2), fortuitous (3), and unknown (3). Regarding location 8 were located on the right and 6 on the left gland. The size of the lesion at diagnosis was 11.15±4.1 cm (range: 5.4–21 cm). Cortisol production was found in 7 cases. At the time of diagnosis, 4 had metastases (liver and/or lung). Only one case could not be intervened due to disseminated disease. After surgery, 5 developed local recurrence and 3 distant metastases. For 2 patients we do not have data regarding post-surgical evolution. Regarding need for post-surgical treatment: 4 patients were not treated for low aggressiveness, 1 for disseminated disease at diagnosis and 1 for post-operative death. 1 patient received adjuvant treatment with Mitotane and 5 Mitotane+etoposide, doxorubicin, and cisplatin (EDP). Only 3 patients have cure criteria today after more than 10 years of diagnosis, 7 patients with a mean survival of 9.3 months (range 3–12) have died, 1 patient has lost follow-up and 4 follow-up reviews of which 2 of them have metastatic disease (at 4 and 20 months post-surgery) and the other 2 are free of disease at this time (at 7 and 38 months post-surgery).
Conclusions
ACC is a very infrequent and aggressive entity in which is necessary to maintain an important degree of alertness and, above all, multidisciplinarity.

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EP15

High blood pressure due to pheochromocytoma: 8 cases

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Introduction
Pheochromocytomas are rare neuroendocrine tumors arising from chromaffincells of the adrenal gland or extra-adrenal paragangliomas. These tumors cause a hypersecretion of catecholamines, resulting in high blood pressure (HBP) and eventual cardiovascular complications. The point of this study is to go through the different clinical aspects of high blood pressure related to pheochromocytomas.
Methods
This is a retrospective study about 8 patients, hospitalized in the internal medicine department in Mahdia, having suffered from a HBP due to a pheochromocytoma , on a period of 13 years.
Results
The study concerned 4 women and 4 men with a mean age of 47.3 years old (33–64). The circumstances under which the pheochromocytoma was discovered, were adrenal incidentaloma in 4 cases and a paroxysmal HBP with adrenergic symptoms in the 4 others. A history of HBP was found in 3 patients. A grade 3 HBP was found in 7 patients with systolic hypertensive peaks reaching 250 mmHg. One out of these 8 patients had a cardiomyopathy and a hypertensive retinopathy due to HBP. The diagnosis of pheochromocytoma was made based on elevated levels of metanephrines in urine in 7 patients and in blood in one patient. CT scanning localized the tumor in 7 patients, while the eighth required an MIBG scan. The tumor was localized in the left adrenal gland in 4 cases , in the right adrenal gland in 3 cases , while an ectopic localization was found in one patient, precisely in the inferior pole of the right kidney. The mean size of the pheochromocytoma was 6.3 cm [3.6–9.8 cm]. The search for a multiple endocrine neoplasia came back negative. All the patients underwent surgery, consisting of a unilateral adrenalectomy in 7 patients. The evolution was marked by the regression of the adrenergic signs and the normalisation of blood pressure without resorting to a medical treatment.
Conclusion
Pheochromocytoma is a rare cause of HBP. The diagnosis must be suspected when faced with a severe paroxysmal HBP, with hypertensive peaks and especially when associated with adrenergic signs. Its diagnosis is based on the measuring of metanephrines in urine or in blood. The surgical treatment may heal HBP.

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EP16

An unusual lesion mimicking adrenal malignancy

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Case report
Adrenal pseudocysts are rare bening lesions that usually mimick solid tumors on imaging. Although they are asymptomatic and often discovered incidentally, distinguishing them from clinically important adrenocortical masses may be problematic before surgery. We report the case of a 50-years-old female who was referred to endocrinology outpatient clinic with a 54×58×50 mm sized mass in the left adrenal gland. Abdominal MRI which was performed because of right flank pain has revealed a Type 3 hepatic hydatid cyst and a lobulated margined adrenal lesion. A differential diagnosis of pheochromocytoma, adrenal carcinoma, and metastatic disease was suspected cause adrenal lesion showed high-signal intensity on the T2-weighted image, and an intense enhancement after contrast. The medical history was unremarkable. The patient was normotensive, no cushing or virilization sign was noted on physical exam. Hormonal work-up indicated a non-functional lesion with a suppression on 1 mg Dexamethasone test, normal aldosterone/renin ratio, and normal levels of urinary metanephrines. DHEAS levels were also in normal range. A significant FDG accumulation was not present at PET-CT imaging. An uneventful laparoscopic surgery was performed based on radiological features of the lesion suggesting a primary adrenocortical malignancy, and a 5 cm mass was excised. Histological examination reported a cyctic cavity with necrotic debris, fibrin and blood costs and a cyst wall with hyalinized fibrous tissue and atrophic adrenal tissue without a clear lining epithelium or endothelium in adrenal gland. A distrofic calcification area was also observed in the lesion. A multidisciplinary team approach is essential for the diagnosis and management of adrenal lesions; surprising results are pleasing especially in those seen really rare as in this case.

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EP17

A case of ACTH-independent Cushing's syndrome caused by bilateral macronodular adrenal hyperplasia

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A 40-year Caucasian female referred to Diabetes centre in November 2016. Her main complaints were 20 kg weight gain over the past 4 years, muscle weakness, high blood glucose readings, high blood pressure (up to 180/100 mmHg),menstrual irregularity.
Medical history
She was diagnosed with T2DM at the age of 39 year. She did not take any blood glucose lowering medication. Her blood glucose readings were: 12 mmol/l at fasting, 20 mmol/l postprandial. She was taking losartan 50 mg/day and bisoprolol 2.5 mg/day for her hypertension regularly. The patient had no family history of endocrine disorders.
Physical examination
Her BMI was 33 kg/m^2. Examination revealed central obesity, buffalo hump and red striae of skin located on the inner surface of the right thigh.
Laboratory findings
Her HbA1c was 9.91%
Plasma potassium level 3.47 mmol/l
Overnight dexamethasone suppression cortisol 488 nmol/l
24 h urinary free cortisol 1877.12 nmol/24 h
ACTH was less than 5 ng/ml
DHEAS 10.5 μmol/l
FSH 5.28 U/l; LH 2.99 U/l
Chromogranin A 45.8 μg/l
Aldosterone: renin ratio 0.4
Abdominal CT
Axial pre-contrast CT image of the left adrenal showed 3 masses: 30×35 mm (22 HU), 19×16 mm (16 HU), 17×17 mm (18 HU). At the right adrenal 2 masses were found: 16×18 mm (26 HU), 10×10 mm (−18 HU). The masses enhanced 60 s after rapid IV contrast bolus to +54 HU, +84 HU, +61 HU, +96 HU, +63 HU; after a 10-min delay, the contrast washed out of the masses to +38 HU, +49 HU, +49 HU, +43 HU, +32 HU (approximately 50%, 56%, 30%, 75%, 38% washout) respectively. The diagnosis of ACTH-independent Cushing`s syndrome, bilateral macronodular adrenal hyperplasia, steroid diabetes, secondary arterial hypertension, secondary amenorrhoea was established. Treatment was adjusted accordingly: glulisine 18 IU/day, glargine 100 IU/ml 20 IU/day. Losartan 100 mg/day, bisoprolol 2.5 mg/day, potassium supplements. After obtaining a satisfactory control of glycemia and blood pressure the patient was succesfully submitted to the left retroperitoneoscopic adrenalectomy (Saint-Petersburg's Clinic of High medical technologies named after N. I. Pirogov). The histology showed adrenal macronodular hyperplasia. Cortisol following the surgery was 32 nmol/l. During the first 6 months, the patient required replacement therapy (hydrocortisone 15 mg/day). The operation led to a complete clinical remission (withdrawal of hypoglycemic and hypotensive medications). Follow-up of the patient (low-dose dexamethasone suppression test annually, CT scans) showed no deterioration of the condition and no growth of masses in the right adrenal gland.

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EP18

Adrenal adenoma with hyperandrogenism and virilization in a postmenopausal women

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Hyperandrogenism and virilization are infrecuent in postmenopausal women and may result from androgen-producing tumors. Androgen-secreting adrenal tumors are rare in clinical practice and often diagnosed as adrenocortical carcinoma, while benign androgen-secreting adrenal tumors are even more rare.
Case presentation
A 63-year-old postmenopausal woman in follow-up for hypothyroidism reported hair loss, increased libido accompanied by deepening of the voice of more than 6 months of evolution. On physical examination she had a body mass index of 25 kg/m^2 and androgenic alopecia. There was no acne, hirsutism, clitoromegalia or other virilization signs. Findings on examination of the neck, breasts and abdomen were unremarkable. She had no signs of Cushing syndrome. Hormonal evaluation showed elevated serum androstenedione 3.2 ng/ml (reference value 0.3–2.7) and 17-hydroxyprogesterone 2.5 ng/ml (reference value 0.3–1). Nugent test, testosterone and dehydroepiandrosterone sulfate were within the normal range. Imaging examination showed nodule of 2 cm in diameter in the left adrenal gland with 13 Housfield units (HU) , wash out 98% and normal appearance of both ovaries. In addition the transvaginal gynecological ultrasound was normal. The patient develop low back pain and an adrenal CT scan was performed, showing adrenal nodule of 3 cm of 6 HU and wash out of 40% (indeterminate origin) Thus, adrenocortical carcinoma was suspected and then adrenalectomy was indicated. After two month and without surgery, she refered alleviated of manifestations of hyperandrogenism, additionally the level of androgens returned to normal range and the adrenal nodule was reduced to 2 cm (with 3.7 HU and wash out of 84%). A PET–CT with FDG confirmed a round nodule in the left adrenal gland and the SUV max of the nodule was 2, considering the possibility of benign adenoma and excluded ovarian abnormalities and other ectopic tumors. In the 3-year follow-up she was asymptomatic and the adrenal image remained unchange. In retrospect it was interpreted that she had a bleeding or necrosis in a virilizing adrenal adenoma that determined the clinical, biochemical and imaging changes.
Conclusion
The androgen source in women with hiperandrogenism and signs of virilism may be the ovary or adrenal gland. The elevated androstenedione and 17-hydroxyprogesterone indicated an adrenal origin. Despite being infrequent adrenal adenomas must be considered as a cause of hyperandrogenic syndrome.

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EP19

Differences between bilateral and unilateral adrenal incidentalomas

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Introduction
Incidentally discovered adrenal incidentalomas has been reported to be as high as 5% of abdominal cross-sectional imaging performed for reasons unrelated to the adrenal gland. Although the management of bilateral and unilateral incidentalomas is the same, some studies suggest differences between the two groups.
Patients and methods
Retrospective study including 91 patients with adrenal incidentaloma at the Department of Endocrinology, Charles Nicolle hospital.
Results
Comparing the group of bilateral incidentaloma (23 patients) to the group of unilateral incidentaloma (68 patients) we found high sex ratio for the first

group (1.55 vs 0.94). The average age was the same for the 2 groups (61 years old). The first group showed more diabetes (47% vs 37%) and less hypertension and dyslipidemia (43% vs 65%). Incidentalomas were revealed more often for the first group with CT scan and less often with Ultrasound and MRI (34% vs 41%). Tumors diameter on average was less in the bilateral incidentaloma group (18.8 mm vs 23.3 mm). Bilateral incidentalomas were associated with a significantly higher prevalence of subclinical Cushing syndrome (26% vs 10%) and a lower prevalence of hyperaldosteronism (17% vs 30%), compared with unilateral lesions, while rates of pheochromocytoma were similar in both groups (4%). Only one patient with bilateral incidentaloma underwent adrenal surgery versus 5 patients with unilateral lesion.
Conclusion
Although patients with bilateral incidentalomas undergo the same management as the patients with unilateral lesions, bilateral incidentalomas are more likely to be associated with subclinical Cushing syndrome and less likely to be hyperaldosteronism.

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EP20

Infertility in woman with classic congenital adrenal hyperplasia

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Introduction
Congenital adrenal hyperplasia (CAH) represent a group of diseases in steroid biosynthesis, due to an enzyme lack in the transformation of cholesterol to cortisol. Women with menstrual dysfunction responds well to adrenocortical inhibition with prednisone, and the significant improvement of menstrual regularity is frequently noted. We report a case of successful pregnancy in a patient with CAH for the first time.
Case presentation
A 35-year-old woman with simple virilising form presented with amenorrhea and secondary infertility. Initialy, in 2013 she was diagnosed with secondary amenorrhea by polcystic ovary syndrome, and received for 3 years treatment with estrogens and progestatives. In 2016 the complete endocrine evaluation revealed a classic congenital adrenal hyperplasia based on high level of 17OH-progesteron and dynamic tests positive. The treatment was based for the next 4 years by Dexametasonum 0.5 mg/day and in September 2019 the pregnancy was confirmed by gynecologist. She was continued the treatment with prednisolone during pregnancy. Now she had 29 weeks of pregnancy and the fetus is monitorized very carefully by the gynecologist. There was a mild increase in the dose of prednisolone during pregnancy. There was no worsening of insulin resistance despite prednisolone administration. The baby is a boy on the genetic evaluation.
Conclusions
The correct diagnosis of female infertility should include the evaluation of 17OH progesterone for the application of a correct treatment that can lead to a pregnancy with normal evolution in women with 17 hydroxylase deficiency.

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EP21

Singularities of the undertreatment of congenital adrenal hyperplasia in adults

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Introduction
Congenital Adrenal Hyperplasia (CAH) results from enzymatic defects caused by autossomal recessive hereditary mutations characterized by deficient cortisol synthesis and, in most cases, increased androgen synthesis. 90–95% of the cases are originated by deficits in 21-hydroxylase and, in about 75% of the cases, there is evidence of mineralocorticoid deficiency.
Case report
A 37-year-old patient was referred to an Endocrinology department due to class III obesity and insulin resistance. He had assistance in another institution for leukocytoclastic vasculitis under therapy with prednisolone 20 mg once a day, with irregular compliance. The patient had history of precocious puberty with appearance of secondary sexual characters at an early age, short stature and familiar consanguinity. Additionally, he had history of infertility. At the age of 35, the patient performed nephrectomy and right adrenalectomy for suspected renal tumour formation. Histological study revealed ectopic adrenal cortical adenoma with 3 cm and a 3 cm adrenal myelolipoma in the right adrenal gland. In the physical examination at endocrinology department, the patient had cervical and axillary acanthosis; skin hyperpigmentation; centripetal obesity; retractable, small and hard testicles; small penis with little hairiness. Initial biochemical and hormonal evaluation showed the following results: 17-OHP 57 ng/ml (0.6–3.4); renin 181 μU/ml (7–76); ACTH 1351 pg/ml (9–52), cortisol 1.7 μg/ml (5–25), Na+ 138 mEq/l e K+ 4.5 mEq/l, FSH 0.5 mUI/ml (<15); LH <0.1 mUI/ml (<9) and testosterone 0.7 ng/ml (2.7–11). These results were consistent with CAH and hypogonadotrophic hypogonadism. An abdominal CT was performed, identifying a 28 mm myelolipoma and two adenomas in the left adrenal gland. Additionally, a scrotal ultrasound revealed an 8 mm hypoechogenic nodular formation in the left testis. This finding, in association with a negative measurement of βhCG and α-fetoprotein, established the diagnosis of testicular adrenal rest tumor (TART). A genetic analysis confirmed the diagnosis of CAH with the identification of the variant g.655C>G of the CYP21A2 gene in homozygosity, with an enzymatic activity of 0–1%. The patient is monitored under hydrocortisone, fludrocortisone and testosterone replacement therapy.
Conclusion
The present case report illustrates the possibility of a late-diagnosed CAH in the context of bilateral adrenal incidentalomas and infertility. The patient developed chronic complications related to late diagnosis and undertreatment. The association of adrenal nodular lesions (mainly myelolipomas) and TART in undertreated CAH patients seems to be related with chronic hyperstimulation by elevated androgens and ACTH. Both fertility and adrenal glands could be preserved with early diagnosis and glucocorticoid treatment.

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EP22

A case of hypokalemic paralysis in a young hypertensive man

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Background
Hypokalemia can be caused by decreased intake of potassium or by excessive loss of potassium in the urine or through the gastrointestinal tract. Severe and life-threatening hypokalemia is defined by levels below 2.5 mEq/l and can be associated with muscle weakness, cramping, headaches, palpitations, polydipsia and polyuria. Periodic paralysis is a very rare presentation in Caucasians.
Case presentation
A 50-year-old Caucasian man, without previous medical history, presented in the emergency department for quadriparesis with predominantly brachial diparesis and hypertensive crisis (220/100 mmHg). Native cerebral computed tomography (CT) was normal. However, biochemical testing revealed severe hypokalemia (1.4 mEq/l), hypernatremia (149.2 mmol/l), high creatine-kinase (5273 U/l), lactate dehydrogenase (2185 U/l) and transaminases (ALT = 106 U/l, AST = 191 U/l), low eGFR (60.24 ml/min per 1.73 m^2) , a raising troponin (from 0.94 ng/ml up to 1.45 ng/ml) and elevated inflammatory markers. Arterial blood gas revealed metabolic alkalosis (pH = 7.56, HCO3- = 36.7 mmol/l). Clinically, he presented with brachial motor deficit, hyporeflexia of the lower limbs, orthopnea, dyspnea and bilateral leg edema. Potassium supplementation was started both intravenously and orally and the patient was transferred to our Endocrinology department, with the suspicion of primary aldosteronism (PA). The patient admitted a long history of high blood pressure, which he had neglected and had never sought medical advice. Plasma aldosterone concentration to direct renin concentration ratio (ARR) confirmed the suspicion (plasma aldosterone = 32.3 ng/dl; direct renin = 0.8 μUI/ml; ARR = 40.3). Consequently, an abdominal non-contrast CT was performed, which showed bilateral adrenal macroadenomas (14/13 mm on the right gland and 12/10 mm on the left gland). Since adrenal venous sampling is not available in our center, we started medical therapy with Spironolactone (150 mg/day, which was gradually reduced to 50 mg/day). Because the patient presented signs of left ventricular dysfunction, we also

added Furosemide (40 mg/day). For further blood pressure control an ACE inhibitor, a calcium channel blocker and clonidine were also introduced. Six-month follow-up showed good control of blood pressure and potassium level, occasional paresthesia in the upper limbs and symmetrical gynecomastia.
Conclusion
Hypokalemic paralysis is a rare form of presentation and the suspicion of PA may be easily overlooked, as it mimics hypokalemic periodic paralysis, polymyositis, Guillan-Barre syndrome. Screening for PA is recommended for any case with spontaneous or diuretic induced hypokalemia and hypertension. Disease control can be obtained with spironolactone, however, the unpleasant side effects in men may lead to low compliance to treatment.

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EP23

Pseudoglandular myxoid adrenal cortical adenoma and secondary hyperaldosteronism

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Myxoid adrenocortical adenoma is a rare adenoma originated from adrenal cortex. A 51 years old male patient was admitted to our hospital due to hypertension and hypokalemia. He has a long history of nonregulated hypertension despite multiple antihypertensive medications. Hypokalemia was detected in last two years with potassium levels around 3.0 mmol/l on high supplementation dose up to 10–16 g of KCl/day. He is obese in the past 10 years. His family history was positive for diabetes (mother) and negative for hypertension. On addmition his blood pressure was 180/90 mmHg, pulse 92/min. Ambulatory blood pressure monitoring (ABPM) showed the mean blood pressure during the day of 159/88 mmHg, pulse 91/min, and during the night 158/85 mmHg, puls 79/min, without diurnal pattern. On 15 g of KCl/day, potassium level was 3.3 mmol/l, with 24 h urinary potassium 225 mmol/24 h. His urinary noradrenaline was above the upper limit (600.1 nmol/l, normal <570 nmol/24 h), while adrenaline (6.2 nmol/24 h) and dopamine (2017.3 nmol/24 h) were normal. Markers of neuroendocrine secretion CgA (23.9 ng/ml) and NSE (6.7 ng/ml) were normal. In LDDST cortisol was suppressed on 77 nmol/l. Testing of the RAAS showed high aldosterone as well as high plasma renin activity (aldosterone >1400 ng/l; PRA 12.1 ng/ml per h; K 4.0 nmol/l). Abdominal ultrasound, CT scan and MR describe hypervascular tumor in the right adrenal, 50×34×36 mm, ddg adrenal adenoma/pheochromocytoma. After premedication with phenoxybenzamine, patient was referred to surgeon who performed right adrenalectomy. Histopathological study showed several growth and distribution patterns. The dominant pattern was presented by cuboid, clear, eosinophilic cells with regular nucleus that were arranged in anastomosing and pseudoglandular patterns, within an abundant myxoid stroma. Immunohistochemical examination showed positivity of the tumour cells for CK AE1/AE3, CD56, inhibin and melanin A. Ki67 was 3%. EMA, CK20, CK7, calretinin and synaptophysin were negative. Weiss score:1. Dg: Pseudoglandular myxoid adrenal cortical adenoma. Postoperative testing showed normal urinary catecholamine levels, normal potassium and normal aldosterone levels with upper normal PRA (K 4.0 mmol/l; aldosterone 38.1 ng/l; PRA 6.49 ng/ml/h. ABPM on Ca-channel blocker, β-blocker and sartane showed normal diurnal pattern with the mean blood pressure during the day of 128/73 mmHg, pulse 69/min, and during the night 103/59 mmHg, puls 59/min. Up to present, 57 cases (24 cases of myxoid adrenocortical adenomas, 2 cases of borderline myxoid adrenocortical neoplasms and 31 cases of myxoid adrenocortical carcinomas) have been reported. Among them, 24 cases of these tumors were pseudoglandular pattern.

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EP24

Case report: Heterochronous Conn's syndrome and a possible Cushing syndrome developed from bilateral adrenal masses, 5 years apart

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Background
Primary hyperaldosteronism or Conn's syndrome is one of the adrenocortical causes of hypertension, alongside hyperdeoxycorticosteronism, apparent mineralocorticoid excess and Cushing syndrome. The two types of hypertension-inducing adrenocortical syndromes (Conn's and Cushing) are extremely rare to be decribed in the same patient. We describe a case of a patient with clinical and biochemical evidence of Conn's syndrome due to a left adrenal adenoma, who developed, 5 years after left adrenalectomy, a potential contralateral cortisol secreting adrenal adenoma.
Case presentation
A 50 year old woman that initially presented in our clinic with severe hypertension, palpitations and headaches had undergone a CT scan 2 years prior which showed an adrenal adenoma, but no other further investigations were performed. The clinical examinantion showed severe obesity (BMI=41 kg/m^2) and uncontrolled hypertension on 4 hypotensors. Laboratory tests: potassium level=3.3 mmol/l, plasma aldosterone concentration (PAC)=188 pg/ml, plasma renin (PR)=2.6 pg/ml, with a ratio of PAC to PR of 72 (≥ 20). The patient underwent laparoscopic left adrenalectomy in 2015, the histopathological examination showing reticular and glomerular hyperplasia. Post-surgery there was a slight decrease of the blood pressure and normalisation of aldosterone and renin levels with normal basal cortisol. Two years later, in 2017, at the annual evaluation, the patient underwent another CT scan, which revealed an adenoma of 1.02 cm/ 2.01 cm on the right adrenal gland. In January 2020, at the re-evaluation, the patient described frontal headaches and also had higher blood pressure since the last visit. We discovered that the right adrenal mass had similar dimensions, but the ACTH levels decreased and the basal cortisol levels were higher (plasma cortisol at 0800 h=24.5 μg/dl). The overnight 1-mg dexamethasone suppression test (DST) was performed, which showed a level of cortisol just under the cut-off point, but close to the upper threshold of the test (1.78 μg/dl vs 1.8 μg/dl). Considering the possibility of the right adrenal mass to determine an ACTH-independent hypercortisolism, the next follow-up will be after 6 months when the 2×2 mg DST will be performed and also the 24-hour urinary free cortisol or late-night salivary cortisol will be assessed.
Conslusions
This case emphasizes the importance of long term follow-up of each patient with endocrine-related hypertension from the clinical point of view (palpitations, headaches, higher blood pressure, muscle weakness, etc.) and also from the hormonal point of view – for aldosteron, renin but mainly cortisol level.

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EP25

Plasma metanephrines and normetanephrines: Alternative indices of avs in a patient with primary aldosteronism and endogenous hypercortisolemia

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Background
Adrenal venous sampling (AVS) is the gold standard method that evaluates the source of aldosterone overproduction in primary aldosteronism. During AVS aldosterone and cortisol are simultaneously measured in order to assess successful adrenal cannulation and lateralization of aldosterone overproduction. However, in patients with both adrenal cortisol and aldosterone overproduction, plasma metaneprhines and normetanephrines can be measured to overcome selectivity and lateralization problems, due to endogenous hypercortisolemia.
Aim
Measurement of metanephrine and normetanephrines during AVS to estimate correct adrenal veins catheterization and lateralization in a patient with both adrenal cortisol and aldosterone overproduction.
Case report
A 60-year-old female with bilateral adrenal adenomas of 3.7 and 4.7 cm presented with hypokalaemia and hypertension. Hormonal work-up showed autonomous aldosterone (aldosterone post-saline infusion test 1910 pmol/l) and cortisol secretion (cortisol post-dexamethasone suppression test 309 nmol/l). AVS without ACTH-stimulation was performed in order to establish the source of both aldosterone and cortisol overproduction, with concomitant measurements of cortisol, aldosterone, plasma metanephrines and normetanephrines from both adrenal veins and inferior vena cava. A

metanephrine selectivity index (SI) of ≥12 was used to determine successful catheterization[1]. A lateralization index (LI) of ≥2.0 [the ratio of the dominant over the nondominant aldosterone/cortisol (A/F) or aldosterone/metanephrine (A/M)] was used to confirmed lateralization of aldosterone excess[2]. The metanephrine-derived SI in right and left adrenal veins were 29 and 12.40, respectively, confirming the correct cannulation. When cortisol was used for lateralization, A/F ratio was similar on both sides and periphery (0.014 right vs 0.014 left vs 0.01 periphery). In contrast, with metanephrine as the denominator (A/M), aldosterone production lateralized to the left adrenal vein (4.28 right vs 11.85 left), with a ratio of 2.8. The same results occurred when plasma normetanephrines were used to calculate LI (ratio≥2.0). Furthermore, the cortisol/metanephrine (F/M) ratio was more than twice in left adrenal vein compared to the right ratio (843.3 vs 293.2), suggesting a left adrenal source of hypercortisolism.

Conclusions

Plasma metanephrines and normetanphrines on AVS are alternative useful markers for the diagnosis and subsequent treatment decision of a patient with bilateral adrenal adenomas overproducing aldosterone and cortisol.

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EP26

Success rate of adrenal vein sampling: A ten-year experience

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Introduction

Adrenal vein sampling (AVS) is the gold standard test to distinguish between unilateral adenoma and bilateral hyperplasia in primary hyperaldosteronism. This is a technical complicated procedure with a variable success rate. Our aim was to report our 10-year-success rate and results as regards to this procedure.

Material and methods

Retrospective observational study including data from patients undergoing AVS between 2009 and 2019.

Results

Data from 15 patients, 7 women and 8 men (48.1±5.5 years old, BMI 33.7±5.23 kg/m^2, blood pressure 157.3±13.1/94±10.2 mmHg) were analyzed. Previous diagnostic imaging tests (Computerized Tomography/Magnetic Resonance Imaging) showed 5 unilateral adrenal adenomas, 2 bilateral adrenal adenomas and 8 images were normal. The success rate of AVS was 60% (9/15). AVS showed lateralization in 6 cases (left lateralization in 5 of them) Imaging test-AVS concordance was 67%. 6 patients underwent adrenalectomy, with anatomo-phatological result of cortical adenoma in 4 of them and cortical hyperplasia in 2. Blood pressure after surgery: 137.5±5.2/85±4.47 mmHg. Adrenal veins were not properly catheterized in 6 cases (5 of them due to inappropriate catheterization of right adrenal vein and 1 due to inappropriate catheterization of both right and left adrenal veins). Complications reported consisted on a unique event of adrenal hemorrhage.

Conclusion

AVS is considered to be the gold standard test to determine the subtype of primary hyperaldosteronism. Success rate of AVS is highly variable. In low-volume centres, as ours, percentage ranges between 40 and 70%, therefore our 60% success rate could be considered acceptable.

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EP27

Importance of dehydroepiandrosterone sulfate assessment in males

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Dehydroepiandrosterone sulfate (DHEAS) is a sulfated ester of dehydroepiandrosterone. Studies of large number of males with DHEAS pathology are infrequent.

Objective

To perform an investigation of significance of DHEAS assessment in males of different ages.

Subjects. Methods. Results

We analyzed clinical data of 3533 patient's (3013 females and 520 males) from DHEAS assessment lists of Vilnius and Kaunas university hospitals. For comparison purposes, a cohort of women was also clinically investigated. DHEAS was assessed 1.6 – 13.5 times more frequently in women than in men. A peak of DHEAS test for women was around 25 years. In males, referrals for DHEAS were uniform during decades, excepting being lower in 0–9 and >75 ages. DHEAS levels in 10- to 24-year-old females were higher than in males. From birth to 9 years and after 45 years, DHEAS was statistically significantly higher in males. Analysis of 491 case records showed low DHEAS in boys, aged 0–9 years and in men, aged 65 – 84. High DHEAS was detected as a peak at around 30 years, but never after 55. Double peak distribution of normal values was evident, with one peak at 10–19 years and a second large peak at 45–64 years. In patients with low DHEAS prevailed congenital adrenal hyperplasia – 31.3%, adrenal tumors (AT) – 29.8% and adrenal insufficiency – 19.3%. High DHEAS prevailed in patients with arterial hypertension – 26.4% and overweight/obesity/hypothalamic dysfunction –18.8%. We found 71 women and 117 men with adrenal tumours (AT). Higher frequency of AT was observed in women around their 30-ties. A peak of AT frequency in men was around 70-ties. We analyzed a list of 3700 consecutive abdominal only and complex abdominal, chest and pelvic computer tomographies (CT) for the age and gender of this examination. Our hypothesis, that referral for CT was much later in men than woman was strongly rejected: peak performance of CT in men and women was the same- between 65 and 74 years of age. In summary, in males, low DHEAS was found in patients with congenital adrenal hyperplasia, AT and adrenal insufficiency. AT were found in elderly and old patients with low or low normal DHEAS. Coincidence of high DHEAS and adrenal tumours was exceptionally rare. In contrary, hypertension and overweight/obesity/hypothalamic dysfunction prevailed in the group of younger patients with high values of DHEAS. This study gives some insight into gender differences of DHEAS secretion in different ages and in adrenal tumours.

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EP28

Conn's adenoma in *post-partum*

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Introduction

Primary hyperaldosteronism is the first cause of secondary hypertension during pregnancy. The diagnosis is too difficult due to the changes in the renin angiotensin system.

Observation

We report the case of a 37 years old women with a history of pre-eclampsia during her pregnancy who consulted the emergency 20 days after delivery for severe hypertension (23/11) and severe hypokalemia (2.2 mmol/l) resistant to intravenous treatment. The aldosterone level was at 2668 pmol/l and the renin level was <0.5 mUI/l with a high ratio at 534 (n<64) confirming the diagnosis of primary hyperaldosteronism. A CT-scaan identified an adenoma in the left adrenal gland with low density at 5 UH. The patient received spironolactone at the dose of 50 mg per day and we noticed a fully correction of hypokalemia and a normalization of the blood pressure. Then a laparoscopic adrenalectomy was performed. On the examination of the removed left adrenal gland , the adenoma appeared well circumscribed yellow, 12×18 mm in diameter.

Conclusion

Despite the fact that Conn's adenoma is a rare pathology during pregnancy, it needs to be indentified sooner to avoid maternal and foetal complications.

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EP29

Testicular adrenal rest tumor (TART) in congenital adrenal hyperplasia misdiagnosed as Leydig cell tumor

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Congenital adrenal hyperplasia (CAH) is a common autosomal recessive genetic disorder. Impaired cortisol production leads to increased adrenocorticotropic hormone (ACTH) levels. Testicular adrenal rest tumor (TART) is a complication of CAH. It is a rare clinical condition usually presented as testicular masses. TARTs may be misdiagnosed as testicular Leydig cell tumors. We report a case of congenital adrenal hyperplasia (CAH) due to 11-beta hydroxylase enzyme deficiency who underwent left orchiectomy for testicular tumors and took a diagnosis of Leydig cell tumor. A 44 year old male born to a consanguineous marriage took a diagnosis of CAH due to 11-beta hydroxylase deficiency at age 10 while being investigated for high blood pressure and short stature. His height was 140 cm, weight was 58 kg and had left gynecomastia. He had two brothers one with CAH. He was taking 5 mg amlodipin and his blood pressure was normal. While using methylprednisolon until very recently he had been started dexamethasone for the high levels of ACTH. After using dexamethasone for 4 months he admitted to our clinic with complaint of excess weight gain. His ACTH level was 259 pg/ml. His therapy was changed to hydrocortisone. After he was started to hydrocortisone therapy his weight gain stopped. The patient came to control after 1 year. He had complaints of testicular pain and darkening of his skin at face. His ACTH level 1858 pg/ml. A scrotal ultrasonography was performed; 4 hypoechoic, highly vascularised testicular masses were detected; the biggest was 10×6 mm in diameter. His alpha-fetoprotein and beta-HCG levels were normal. The patient admitted to the urology clinic, left orchiectomy was performed. The patient came to our clinic with his pathology report which was consistent with Leydig cell tumor. Thinking possibility of a TART the pathology report was asked to be reviewed again and the report was revised as TART. In immunohistochemical study CD56 staining was focal positive, inhibin was strongly positive, calretinin was weakly positive and androgen receptors were negative supporting TART. He has been started low dose dexamethasone therapy. His ACTH level was 256 pg/ml after 0.25 mg/day dexamethasone therapy. It is important to distinguish Leydig cell tumors from TART in patients with CAH.

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EP30

The utility of pre-test cortisol and other parameters in the prediction of short Synacthen test failure

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Introduction
Short Synacthen tests (SST) are expensive, inconvenient, time consuming and subject to Synacthen availability. Any strategy reducing the need for SSTs will improve its cost effectiveness and also improve patient satisfaction. In this regard indications for SST and assay specific pre-test cortisol levels (not all SSTs are done at 0900 h) may have clinical utility.
Methods
We retrospectively examined the indications for, time and place of testing, and the utility of pre-test cortisol concentrations of all SSTs done in the Aneurin Bevan University Health Board over a period of 12 months. Receiver-operating characteristic (ROC) curve analysis was undertaken for pre-test cortisol to obtain a cut off value for failure.
Results
We analysed 506 SSTs of which 106 (21%) were abnormal. SST failure was highest for the indications of "current therapy/weaning from steroids, and low random cortisol levels" (39.6%; $P<0.001$). There was no difference in outcome for indications such as hyponatraemia, postural hypotension and tiredness/fatigue. Median pre-test cortisol (interquartile range) were significantly different in those with abnormal SSTs compared to those with normal SSTs [147 (91–213) vs 298 (227–393), $P<0.001$]. There was a higher test failure rate in those who had an early morning SST compared to others (26.8 vs 19.5%, $P=0.001$); but there was no difference when place of testing was compared (outpatient or inpatient). ROC curve analysis indicated SST failure with 100% sensitivity with pre-test cortisol of <47 nmol/l; and a normal SST with 100% specificity with cortisol >323 nmol/l.
Conclusions
This study indicates that (i) pre-test cortisol levels of <47 predicted SST failure with 100% sensitivity and cortisol of >323 predicted a normal SST with 100% specificity; (ii) in this group 141 tests may have been avoided if these cutoffs were applied with a significant cost saving; (iii) some indications had a higher predictability for SST failure, and those with lower predictability need supporting evidence before SST is undertaken.

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EP31

Expression of CYP11B2 and CYP11B1 immunostaining in primary aldosteronism

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CYP11B2 is a key enzyme of primary aldosteronism, and several factors are involved in the regulation of CYP11B2 expression and the overproduction of aldosterone. Somatic mutations in aldosterone-driver genes are strongly associated with CYP11B2 expression and have been only detected in the CYP11B2-positive tumor area, indicating that aldosterone producing adenoma (APA) intratumoral heterogeneity corresponds to non-uniform CYP11B2 expression in neoplastic cells. In addition, CYP11B2 can contribute to the clinical diagnosis of primary aldosteronism. CYP11B2 has the potential to synthesize hybrid steroids, which is a unique and characteristic behavior of APA that is distinctive from bilateral hyperaldosteronism (BHA). However, the pathophysiology of primary aldosteronism in both APA and non-neoplastic subtypes remains controversial.
Objective
Our aim in the present study was to compare immunohistochemical (IHC) CYP11B2 and CYP11B1 staining in adrenal slices to histological diagnosis based on H&E staining.
Materials and method
Retrospective evaluation adrenal tumors from patients with primary aldosteronism ($n=20$). According to CT unilateral macrohyperplasia was detected in 19 patients (95% of total), all of them were confirmed to have unilateral hyperproduction of aldosterone according to AVS. Both H&E and immunohistochemical expression of CYP11B2 and CYP11B1 (mouse monoclonal anti-human CYP11B2 primary antibodies and rat monoclonal anti-human CYP11B1); were analyzed in 3.5 mm thick adrenal slices in one representative slide from each case. In addition to IHC analysis of aldosterone-producing adenomas (APAs) and hyperplasia, small extranodular CYP11B2 positive cell clusters, so-called aldosterone-producing cell clusters (APCCs) were identified.
Results
Immunohistochemistry studies of the resected adrenals from 20 patients with PA operated due to unilateral production of aldosterone using CYP11B2 and CYP11B1 staining showed that 10 of those with an adenoma on CT scanning showed CYP11B2 and CYP11B1 staining in the adenoma. Furthermore, 5 cases of an unilateral adenoma, showed CYP11B2 and CYP11B1 staining in the adjacent adrenal cortex and an absence of staining for CYP11B2 in the adenoma. 5 cases showed CYP11B2 expression is heterogeneously immunolocalized throughout the tumor area.
Conclusions
Thus, the functional heterogeneity of adrenal tumors in primary aldosteronism has been proven. IHC staining of adrenal tissue improves subtype diagnostics of primary aldosteronism.

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EP32

Nonfunctional adrenal adenoma in practice of the endocrinologist

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Aims
We investigated the clinical characteristics and follow-up findings of subjects with adrenal incidentalomas (AI) in a single, tertiary-care hospital in Yekaterinburg, Russia.
Methods
This study retrospectively evaluated consecutive patients aged 18 years or older with benign AI, not treated with adrenalectomy, which were nonfunctioning (n-56). The initial and follow up evaluation, including clinical assessment, hormonal investigations and imaging were coordinated via a clinic No. 40 in Yekaterinburg.
Results
The median age in patients with *nonfunctional adrenal adenomas* (NFAI) was 64.41±10.62 years old, women – 46 (82.1%), men – 10 (17.9%). The localization of NFAI in the right adrenal gland is – 14 (25%), in the left – 28 (50%), bilaterally – 14 (25%). The plasma cortisol was 462.35±263.31 nmol/l (101.2 – 535.7 nmol/l); plasma aldosterone

–140.21±96.10 pg/ml (25 – 315 pg/ml), urinary fractionated methanephrins (MN) – 131.34±112.73 μg/day (<320 μg/day), urinary fractionated normetanephrins (NM) – 183.86±312.14 μg/day (<390 μg/day). The mean nodule size of NFAI based on computed tomography was 2.44±1.45 cm, the observation period was 5.27±3.05 years. According to CT, the density of formations in the native phase (NP) varied from −69 to +50 HU, median=6±26 HU, in arterial phase (AP) median=72±24 HU, in venous phase (VP) median=55±23 HU, in delayed (DP) (6 min) median=27±11 HU.
Conclusion
Most AIs are hormonally inactive adenomas. The low tumor density on CT scan picture may be predictive of both hormonal activity and the risk of malignancy. The risk of malignancy decreases with the size above 2.44 cm.
Keywords: adrenal incidentaloma, *nonfunctional adrenal adenoma.*

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EP33

Pediatric retroperitoneal paraganglioma with uncommon symptom treated successfully by laparoscopic surgery: Case report and literature review.

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Introduction
Pheochromocytoma and paraganglioma are rare in the pediatric population occurring in approximately 1 in 50 000 children. *The clinical presentation may range from asymptomatic to the classic triad of episodic diaphoresis, headache, and palpitations*. Among hypertensive children, the incidence of surgically confirmed pheochromocytoma or catecholamine-secreting paraganglioma ranges from 0.8 to 1.7 percent. Catecholamine-secreting paragangliomas are often located in the superior and inferior para-aortic areas (75 percent of extra-adrenal tumors); the bladder (10 percent); the thorax (10 percent); and the skull base, neck, and pelvis (5 percent). Surgery plays an important role in managing the disease. Paragangliomas usually require an open surgical approach. Meanwhiles, laparoscopic surgery may be challenging in pediatric patients with paraganglioma especially in retroperitoneal location. We herein report a case of a paraganglioma that was located retroperitoneal area successfully resected by laparoscopic surgery.
Case presentation
We report a 16-year-old male admitted to the hospital due to intermittent generalized tonic – clonic seizures. With recent history of hypertension being treated irregularly with unknown medication. Further evaluation conducted revealed his hypertension was paroxysmal and in accompanied with classic triad of adrenergic symptoms consisting of headache, palpitations, diaphoresis and elevated levels of catecholamines in the blood and urine samples. Abdominal computed tomography revealed a 4×3 cm retroperitoneal mass likely to be paraganglioma. The patient underwent laparoscopic surgery and the tumor was dissected completely with no complications.
Discussion
Incidence rates of pheochromocytoma and paraganglioma are estimated at 0.3 cases per million per year, with approximately 20 percent of cases diagnosed during childhood. In children, approximately 80 percent of catecholamine-secreting tumors are pheochromocytomas and 20 percent are paragangliomas. Seizure without any other neurological diseases is a rare symptom in pediatric paraganglioma. This condition could be a consequence of paroxysmal hypertension. Surgical resection is the primary treatment in which open surgical approach is more favorable in the management of paraganglioma. Moreover, resection of retroperitoneal paragangliomas is often a surgical challenge especially in pediatric population. However, endoscopic surgery has been properly performed in this patient without any complication.
Conclusion
Paragangliomas presented with seizure are extremely rare in pediatric population. Laparoscopic surgery which is a challenging procedure to this patient group was conducted successfully in the present case.
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EP34

Clinical, paraclinical features and outcome of adrenocortical carcinoma

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Introduction
Adrenocortical carcinoma (ACC) is a rare aggressive endocrine neoplasm. It's a heterogeneous malignant tumor with incompletely understood pathogenesis and poor prognosis. The aim of our study was to assess clinical and paraclinical characteristics of ACC and to determine its outcome.
Methods
In a retrospective and descriptive study, we included patients with adrenocortical carcinoma confirmed with histopathological examination. Clinical, biological, hormonal, radiological and therapeutic data were collected.
Results
We included four women and a man with an adrenocortical carcinoma. Their median age was 45.8 years [extremes: 31–60]. Their past medical history included diabetes mellitus, intellectual disability and ovarian teratoma in one case, respectively. Three patients presented with abdominal pain and were referred to our department for the exploration of an adrenal mass. One patient was admitted for clinical signs of Cushing's syndrome and the fifth patient presented with weight loss, asthenia and anorexia. On physical examination, two patients had android obesity, hirsutism, high blood pressure, muscle atrophy, skin atrophy, purple striae and facial plethora. Routine blood tests revealed dyslipidemia and diabetes in two cases and severe hypokalemia at 2.4 mmol/l in one case. Three patients had an active hormone secreting tumor with a Cushing syndrome. Cortisol levels after standard Dexamethasone suppression test were 3.5, 12.6 and 33.5 μg/dl, respectively. Among these three patients, one had mixed hormone secretion of cortisol and androgen. Two patients had hormone-inactive tumor. Adrenal computed tomography (CT) scan revealed a right tumor in four patients and a left tumor in one patient. The tumor had heterogeneous enhancement with central intratumoral calcifications in all the cases. Its diameter varied between 5 and 11 cm. A focal extension into the inferior vena cava, liver and kidney was present in one patient. Surgical treatment was performed to four patients. Only one patient had received mitotane. For the other patient, this drug was not available. Two patients died 6 and 48 months after the surgery, respectively. Two patients showed no signs of recurrence in their last CT scan and one patient was lost to follow up.
Conclusion
ACC is a rare and aggressive endocrine neoplasm that may present when hormonally active or after they have become large. The study of the clinical features could conclude to the type of the secretion. Surgical resection represents the treatment of choice in localized ACC. Mitotane, alone or in combination with other agents, remains the most effective chemotherapy.
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EP35

Mediastinal malgnant paraganglioma: An atypical presentation

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Introduction
Mediastinal paragangliomas are rare. These tumours can be associated with increased morbidity and mortality when invasive growth to the heart, great vessels, esophagus and trachea occurs. Surgical resection, if feasible, is the treatment of choice.
Case report
A 50-year-old man presented with severe and refractory left gluteal pain radiating to the posterior thigh for two months. The patient had no relevant medical history and no other symptoms. Computer tomography (CT) was performed and suggested a metastatic osteolytic lesion in the sacrum and left iliac bone (6×5 cm). Chest-CT identified a large mass involving the right atrial appendage and atrium extending from the right ventricular outflow tract to the diaphragm (13×8.7×7.9 cm). This hypervascular lesion showed close proximity with the heart and great vessels without a clear cleavage plan with these structures. An echocardiogram confirmed the presence of an extra-cardiac mass adherent to the heart without affecting myocardial or valvular function. A cardiac magnetic resonance imaging (MRI) with respiratory gating showed extensive cardiac invasion by the mediastinal tumour, excluding the possibility of surgical resection without heart transplant. A guided biopsy of the iliac mass was compatible with metastatic paraganglioma with Ki67 of 40%. The patient was then referred to the endocrinology clinic. Family history was positive for a non-functioning vagal SDHD in a half-brother, who had undergone surgey 10 years before, as well as father's death with a neck mass. Genetic testing was not performed in proband's brothers at that time. The same SDHD mutation was confirmed in the patient. Functional imaging study with 68Ga-DOTA-NOC showed intense uptake in the known lesions in the mediastinum and sacrum, and also in the left parapharyngeal space. The patient was recently proposed for chemotherapy with Capecitabine and Temozolamide and supportive cardiac treatment. The

iliac-bone lesion was treated with 20 Gray of palliative local radiotherapy (RT) and painkillers, with symptomatic improvement.
Discussion
SDHD mutation is the most frequent familial paraganglioma syndrome and is an imprinted gene, with paragangliomas occurring in patients who inherited the mutation from the father. Genetic counselling and testing of the paternal line may result in earlier diagnosis and treatment of the relatives. Malignant mediastinum paragangliomas associated with heart infiltration and SDHD mutations are extremely rare. Beyond atypical presentation, location and tumor behaviour, this case report highlights the importance of establishing a hereditary syndrome in the proband.
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EP36

Paraganglioma and ulcerative colitis: A case report
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Introduction
Paragangliomas are rare endocrine tumors that represent extra-adrenal localization of pheochromocytomas. Signs of catecholamine excess are the most found manifestation of this tumor especialy hypertension. However, paragangliomas can be asymptomatic or can manifest with nonspecific signs. The association between pheochromocytomas and inflammatory diseases is exceptional.
Observation
Here we report the case of a 26 years old male that was admitted into the internal medicine unit for exploration of arterial hypertension associated with a flush syndrome. The clinical manifestation started five months before his admission. He presented a weight loss with abdominal pain and diarrhea. On the physical exam, the patient had a diffuse sensibility. The diagnosis of pheochromocytoma was highly suspected. Blood investigations revealed an elevation of metanephrines 200 times the normal level but the abdominal scan showed a bilateral retroperitoneal mass. An MIBG scintigraphy demonstrated an intense fixation in the latero-aortic region and the inter aortocaval space. The patient was operated successfully and the diagnosis of paraganglioma was confirmed histologically. However, we noted the persistence of diarrhea so a colonoscopy with biopsy was performed and the diagnosis of ulcerative colitis (UC) was posed.
Conclusion
This is the first case to demonstrate the possible association between ulcerative colitis and paraganglioma. Even though paraganglioma can manifest with diarrhea, inflammatory bowel diseases should be suspected in the absence of amelioration after surgical treatment.
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EP37

Acute low members ischemia revealing a pheochromocytoma
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Introduction
Pheochromocytoma is a rare tumor of adrenal gland tissue that is responsible for secondary hypertension and other clinical manifestations resulting from catecholamine excess and it can result in severe damage to other body systems, especially the cardiovascular system. Here we report an atypical presentation of pheochromocytoma.
Presentation
A 40 years old female patient that was admitted into the internal medicine ward with acute ischemia of lower limbs. The patient has no particular medical history. She had a high blood pressure level (160/90 mmHg) without other signs of catecholamine excess with no hypokalemia. The Doppler ultrasound showed permeable arteries. The angioscan did not show vascular abnormalities but an 11 mm left adrenal adenoma. Biological investigations for an endocrine cause of hypertension showed elevation of plasma metanephrines 5 times the normal levels. The diagnosis of pheochromocytoma was posed and the patient was operated with a positive outcome.
Conclusion
The classic symptoms of pheochromocytoma include palpitations, headache, and generalized sweating. Those signs may occur in a paroxysmal manner. The presence of hypertension in young adults even without the typical presentation should lead us to think of the diagnosis of pheochromocytoma.
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EP38

Intracardiac paraganglioma in a patient with a paraganglioma syndrome type 4. Short, medium and long-term follow-up
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Introduction
Paraganglioma type 4 is the second most common hereditary paraganglioma syndrome. It is due to a mutation in the succinate dehydrogenase B (SDHB) gene. Associated with high morbimortality for presenting high penetrance (77%) and debut at an early age with a high probability of malignancy (31–71%). In terms of follow-up, annual biochemical monitoring is recommended for mutation carriers. However, the affected gene should be taken into account, for example: there is a high morbidity associated with undiagnosed paragangliomas in patients with SDHB mutations, which requires closer monitoring. In addition to biochemical testing, periodic imaging tests should be considered to detect biochemically silent tumors.
Clinical case
62-year-old male, carrier of the c166-170del CCTCA mutation of the SDHB gene. Cardiac paraganglioma is detected by octreoscan in 2015. The left ventricular tumor is resected respecting left ventricle and coronary sine. The anatomic pathology findings are compatible with subepicardial paraganglioma that affects the resection margin. Regarding follow-up, during the first year it is quarterly, using methynephrine catecholamines and methoxytyramine (negative); and with a semi-annual imaging test where a small recurrence adjacent to the coronary sinus is detected in MRI, with uptake in PET/CT, therefore ruling out cardiac surgery. -During the second and third year, semi-annual follow-up with catecholamines and methanephrines (negative) and imaging tests using PET/CT (radiological stability). During the fourth year, semi-annual follow-up by methoxytyramine, catecholamines and methanephrines (negative), and annual imaging tests, with octreoscan (negative) and PET/CT (lack of progression), and findings of a focal increase of metabolism in the right colon that turns out to be a false positive.
Conclusion
Cardiac paragangliomas are exceptional, making up 1% of all cardiac tumors. The most aggressive variant of SDH mutations is SDHB, presenting a 77% penetrance and a malignancy risk of up to 71%. Genetic study of the relatives of an affected individual is essential for an early diagnosis. Monitoring is performed by biochemical determinations of catecholamines and methanephrines and imaging tests (MRI, PET/CT), with a variable periodicity depending on the morbidity associated with the genetic mutation.
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EP39

Pheochromocytoma in genetic disorders
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Introduction
Several familial disorders could be associated with adrenal pheochromocytoma such as Von Hippel–Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN2) and, less commonly, neurofibromatosis type 1 (NF1). Herein, we report three cases of pheochromocytoma as a part of genetic syndromes.
Observations
Patient 1
A 34-year-old women with no familial history, was diagnosed with severe hypertension at 36 weeks of pregnancy. After delivery she was admitted for further exploration of an uncontrolled hypertension and palpitations. The physical examination showed café au lait spots (>6), two *neurofibromas* and clusters of freckles in the armpits and under the breast. Eye exam detected lisch nodules. The diagnosis of NF1 was made. A 24 h urinary test founded a metanephrine level of 17 572 nmol/Cr (normal range 15–120 nmol/Cr) and a normetanephrine level of 6250 nmol/Cr (normal range 40–280 nmol/Cr). Adrenal-CT reveled a right heterogeneous adrenal mass (70×73 mm) with

areas of necrosis. MIBG scintigraphy showed a right adrenal mass with a strong supporting evidence for a pheochromocytoma.
Patient 2
A 25-year-old woman with no familial history, had a surgical resection of a cerebellum hemangioblastoma. Genetic analysis identified a heterozygous germline mutation in the VHL gene consistent with VHL syndrome. Further multiple tumor screening showed bilateral adrenal masses on the CT scans and the functional nature of the adrenal masses was confirmed by a MIBG scintigraphy. Elevated urinary metanephrine level of 1200 nmol/Cr (normal range 15–120 nmol/Cr) and a normetanephrine level of 1484 nmol/Cr (normal range 40–280 nmol/Cr) confirmed the diagnosis of bilateral pheochromocytoma.
Patient 3
A 32-year-old woman with no familial history, was diagnosed with medullary thyroid carcinoma and was treated by a total thyroidectomy. Screening for further tumors revealed bilateral adrenal masses on the CT scans and the Octreoscan detected bilateral adrenal uptake suggesting bilateral pheochromocytoma. Herein, she was admitted to our department for further explorations. The patient was asymptomatic with a normal blood pressure and heart pulse. Biological finding showed an elevated concentrations of plasma chromogranin A of 100 ng/ml and elevated 24 h urinary metanephrine level of 618 nmol/Cr (normal range 15–120 nmol/Cr) and normetanephrine level of 436 nmol/Cr (normal range 40–280 nmol/Cr). We concluded to a diagnosis of MEN2. The serum calcium level, phosphate level and parathormone level was normal.
Conclusion
More than 35% of pheochromocytoma are hereditary. Early diagnosis and regular follow-up are the only means for a better outcome.

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EP40

Persistent hypokalaemia leading to a diagnosis carcinoid lung cancer. A case study

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Background
An 81-year-old gentleman presented to his GP with a 2 week history of reduced appetite, lethargy and 2–3 kg weight loss over the last month. On routine bloods, his potassium was noted to be 2.2 mmol/l. He was being treated in the community with indapamide, losartan and amlodipine for hypertension. He was admitted to hospital for IV replacement. However, he had persistent hypokalaemia (<2.9 mmol/l) for 3 days despite appropriate replacement and suspension of potential medications driving his hypokalaemia. An initial VBG on admission showed a hypokalaemic metabolic alkalosis, and a routine chest X-ray showed a suspicious looking lesion. The follow up CT chest revealed a left lower lobe lesion, consistent with a new malignancy (T2b/N3/M0), with evidence of idiopathic pulmonary fibrosis, bilateral pleural effusions and calcifications. These CT findings raised suspicions of an ACTH secreting small cell lung cancer, despite the patient not having any cushingoid features. His serum cortisol was 398 nmol/l. He had a partial response following an overnight dexamethasone test (cortisol 99 nmol/l). Cortisol levels throughout the day were 342, 357, 301, and 345 nmol/l at 0600 h. Cortisol was suppressed to 76 nmol/l following low dose dexamethasone suppression which was indicative of Cushing's Syndrome. His ACTH was not very high at 9 ng/l. He was referred to the lung malignancy MDT. A PET scan revealed significantly increased uptake of FDG in the 4 cm left lower lobe lung mass, typical of a carcinoid tumour. Tumour histology was positive for ACTH, synaptophysin, chromograffin and CD56 secretion. Proliferation index assessed with Ki67, was <1%. Further blood tests revealed an elevated chromograffin A (76 pmol/l) suggestive of a neuroendocrine tumour. Urine 5-HIAA testing which was positive with a reading of 113, suggestive of carcinoid syndrome. Repeat test was 26. Normal range (5–35). 24 h free cortisol excretion was elevated at 213 mmol/l. He has no other symptoms or signs of carcinoid syndrome: facial flushing, diarrhoea, wheezing, heart failure or Cushing's syndrome. His potassium levels remained stable following medication adjustment, and intervention with steroid synthesis inhibitors was not necessary. He was referred for surgery but unfortunately he was not a surgical candidate due to cardiac issues and anaesthetic risk. In the meantime, he has functionally deteriorated and referred to palliative team.

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EP41

Primary hyperaldosteronism in Cantabria: Clinical and biochemical characterization and outcomes

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Introduction
Primary hyperaldosteronism (PH) is a cause of arterial hypertension (HT). The prevalence ranged from 1 to 15%. PH is associated with higher rates of cardiovascular morbidity and mortality. PH is under-diagnosed. The aims were to know the prevalence of PH, the clinical and hormonal profiles, outcomes, and prognosis of our population.
Material and methods
A retrospective review of patients with primary hyperaldosteronism in our hospital in the last 20 years (1996–2016). We analyzed motive for the screening, HT, CV risk factors and events at the time of diagnosis, aldosterone levels (ALD), plasma renin activity (ARP), RATIO ALD/PRA, and treatment outcomes.
Results
Forty-six patients, 26 men, and 20 women. Age of 52 years (29–81). In 80%, the onset was hypertension with hypokalemia, 17% was severe or resistant HTA, and 3% was hypertension with an adrenal mass. The diagnostic delay was 12 years (0–43). At presentation, 60% HVI, CVD 35%, PAD 22%. DM2 in 13%, obesity in 41%, dyslipidemia 45%. Serum ALD were 49 ng/dl (10.7–134.2 ng/ml), 6% below 15 ng/dl. Mean ARP ng/ml per h was 0.33 (<0.02–1.48). CT or/and MRI were performed at 100%. Adrenal Catheterization in 4 patients. In contrast, functional scintigraphy of the adrenal gland was performed in 35% of patients. Unilateral adenoma in 56.5% and removed surgically. Bilateral adenoma in 4%, and bilateral hyperplasia in 39.5%, both were in medical treatment.
Conclusions
The number of cases is lower than expected. The delay in diagnosis increases vascular morbidity. Our data suggest a level ALD of ≥ 10 ng /dl suspect a PA, lower than that recommended in the guidelines, in line with data from other recent studies. Adrenal catheterization is not a common practice in our environment as a pre-surgery test, instead we perform functional scintigraphy of the adrenal gland. The distribution of the etiological diagnosis is similar to other series.

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EP42

Evaluation of pulmonary function and dyspnea index in Greek COPD patients with at least one metabolic comorbidity versus the population of the study without comorbidities – AEOLOS study

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Introduction
Metabolic disorder has been frequently observed in chronic obstructive pulmonary disease (COPD) patients. In particular, metabolic comorbidities exert a major impact on patients' morbidity and mortality. Diabetes mellitus, dyslipidemia and osteoporosis are among the most commonly reported metabolic comorbidities in patients with chronic lung disease. COPD patients with comorbidities, such as metabolic disease, are generally more dyspnoeic and have worse health status in comparison to patients without comorbidities.
Objectives
We evaluated FEV1 (%predicted) change and MRC dyspnea score in COPD patients with at least one metabolic comorbidity versus the patients without any comorbidity, treated with a fluticasone–salmeterol fixed dose combination (FDC) for 12 months.
Methods
Prospective, multicenter, non-interventional clinical study (NCT02978703) in which 1016 patients, aged 69.54±9.57 with a mean body mass index of 28.65±5.38, were evaluated and of whom 378 (37.2%) had at least one metabolic disease and 238 (23.4%) hadn't any comorbidity. Pulmonary function was assessed by FEV1 (%predicted) changes and MRC dyspnea scores

among visits. The corresponding data were collected at 6 (V1) and 12 (V2) months, respectively.
Results
In the study population without any comorbidity there was a significant improvement ($P<0.0001$) in both FEV1 (%predicted) between baseline (V0) and final (V2) visit, as well as between consecutive visits (V0: Mean±S.D.: 49.90±8.23, V1: Mean±S.D.: 55.95±10.96, V2: Mean±S.D.: 59.16±11.84). Similar significant improvement was observed on the MRC dyspnea scale ($P<0.0001$, Kruskal–Wallis test). In COPD patients with at least one metabolic comorbidity, a corresponding but reduced improvement was observed in FEV1 (%predicted), between baseline and final visit, and between visits [FEV1%predicted: (V0: Mean±S.D.: 47.99±8.85, V1: Mean±S.D.: 54.17±11.43, V2: Mean±S.D.: 56.02±12.12), and on the MRC dyspnea scale ($P<0.0001$, Kruskal–Wallis test) as well.
Conclusions
Patients with metabolic comorbidities and COPD, although they had initially slightly worse pulmonary function and MRC dyspnea score, showed a statistically significant improvement but decreased in relation to COPD patients without comorbidities, after twelve months of fluticasone–salmeterol FDC treatment.

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EP43

Pericarditis complicated with cardiac tamponade and Addison disease – A case report

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Introduction
Addison Disease is a rare condition with an estimated incidence in the developed world of 0.8 cases per 100 000 population. It is associated with relevant morbidity and mortality rates, but once the diagnosis is made it can be easily managed. When Addison Disease is associated with other autoimmune diseases, the diagnosis of polyglandular autoimmune syndrome can be set. The recognition of symptoms and signs can be challenging and clinicians should be aware of atypical presentations, since they can be fatal if not correctly identified.
Case report
A 24-year-old man was admitted to a coronary intensive care unit due to acute pericarditis complicated with tamponade and shock requiring aminergic support. After introduction of methylprednisolone 125 mg twice daily, the condition improved. The patient had history of septic shock 2 months before and episcleritis with 2 years of evolution. One month later, when the patient was on 8 mg of methylprednisolone, a new episode of pericarditis occurred, requiring a pericardial window. An exhaustive study regarding autoimmunity and serologic causes were performed, but no etiology was identified. The patient was discharged under methylprednisolone 32 mg in slow and gradual discontinuation scheme. After four months, when the patient was on methylprednisolone 8 mg, new episode of pericarditis, establishing the diagnosis of recurrent pericarditis. Because the patient had hyponatraemia (126 mmol/l) and hyperkalaemia (6.4 mmol/l), an endocrinological assessment was required. Due to suspected adrenal insufficiency, an analytical and hormonal study was requested, showing the following results: ACTH 172 pg/ml (9–52); cortisol<1 µg/dl (5–25); renin 5306 µU/ml (7–76) and anti-21 hydroxylase antibody 25.1 U/ml (<1). These findings established the diagnosis of autoimmune primary adrenal insufficiency. Moreover, additional autoimmunity assessments requested showed the following results: anti-transglutaminase IgA, anti-TPO, anti-thyroglobulin and anti-intrinsic factor antibodies negative; anti-parietal cell antibody strong positive. The study was compatible with polyglandular autoimmune syndrome. The patient started therapy with prednisolone and fludrocortisone, with clinical improvement without further pericarditis' episodes.
Conclusion
Pericarditis with tamponade was the first manifestation of Addison Disease in this patient. This association corresponds to a rare case, with few cases described in the literature. The early identification of this condition can be life-saving. This patient, after 2 years of follow-up under treatment directed to Addison Disease, did not relapse pericarditis and shock. The presence of unexplained hyponatremia and hyperkalaemia should raise the suspicious of Addison Disease, even in the existence of atypical presentations.

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EP44

Bilateral adrenal adenomas and primary hyperaldosteronism – case report

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Introduction
Primary aldosteronism (PA) is an important cause of secondary hypertension, associated with increased cardiovascular morbidity and mortality rate compared to patients with essential hypertension.
Case report
We report the case of a 59-year-old Caucasian male with a medical history of dilatative cardiomiopathy, paroxysmal atrial fibrillation and bifascicular block who was admitted to the E.R. with shortness of breath, headache, palpitations, blood pressure at 162/117 mmHg and concomitant hypokalemia (2.5 mmol/l). The patient had no clinical signs of cortisol excess. Laboratory tests showed the following: elevated plasma aldosterone at 41.2 ng/dl, supressed renin activity (<0.10 ng AI/ml/h), elevated aldosterone/renine ratio at 420, urinary metanephrines at 141 µg/24 h, 8 h cortisol at 18.5 µg/dl and no supression of cortisol levels by low-dose dexamethasone in addition to low-normal ACTH levels (11 pg/ml). The abdominal MRI scan showed nodules in both adrenal glands (in the right medial of 23/18 mm, right lateral of 12/9 mm, left central of 13/14 mm and left lateral of 7/9 mm). Adrenal venous sampling further evidenced aldosterone secretion from the right adrenal gland (aldosterone/cortisol ratio – right/left was 3.89, 3.65 and 8.17:1). Unilateral right adrenalectomy was performed and the histopatological examination concluded the presence of right adrenal adenomas. The clinical outcome was favorable, with regression of blood pressure values and development of short-term secondary hyperkalemia.
Conclusion
Distinction between unilateral and bilateral secreting adenoma is an important stage and in such cases adrenal venous sampling is essential in diagnosis and establishing case management. In rare instances, cosecretion of aldosterone and cortisol has been reported.
Keywords: hyperaldosteronism, adrenal venous sampling, cortisol

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EP45

GAD antibody associated stiff man syndrome in a young boy with primary adrenal insufficiency

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Background
Stiff Person Syndrome (SPS) is an extremely rare neurological disorder, with an expected prevalence of less than 1 per million. The first described case of SPS in the literature was reported in 1959 by Moersch and Woltman. SPS is featured by progressive muscle stiffness, rigidity, and spasm involving the axial muscles, which may result in severely impaired ambulation. SPS seems to have an autoimmune basis although its exact pathogenic mechanism is still cloudy. Most SPS cases are associated with antibodies against glutamic acid decarboxylase (GAD).
Case report
We report a case of 15 years old boy presented with history of stiffness of upper and lower limbs associated with stiffness of neck with restriction of movements. Initially suspected to have spinal cord involvement or tetany. He had presented to endocrine department 9 years back with easy fatigability, weight loss, giddiness and generalised darkening of skin. He is born out of consanguineous marriage and 1st in birth order among 4 children. He was diagnosed to have primary adrenal insuffiency and was started on replacement. On evaluation, MRI brain and spine were normal. Other blood investigations were normal. GAD antibodies in serum was strongly positive.

Patient was diagnosed to have stiff man syndrome based on clinical and autoimmunity panel which showed anti GAD antibodies strongly positive and ENMG. Patient was treated with IV immunoglobulins and steroids. Recently he was diagnosed to have type 1 diabetes and started on insulin.
Conclusion
In conclusion, this case highlights that an acute gait disturbance syndrome and stiffness in children with primary adrenal insufficiency should raise clinical suspicion of autoimmune diseases and stiff-person syndrome.

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EP46

Metastatic melanoma of unknown primary lesion presenting as bilateral adrenal incidentalomas

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Introduction
Bilateral adrenal incidentalomas represent a challenge both in diagnosis and therapeutic approaches. While initial testing is similar to unilateral adrenal incidentalomas, additional investigations should be made considering the differences between the distribution of etiologies.
Case report
We report the case of a 67 years old hypertensive female, presenting with backpain; an initial abdominal ultrasound described left adrenal mass and a large right adrenal/hepatic mass. The thoraco-abdominal CT scan revealed a well circumscribed right sided adrenal mass (105/95/110 mm AP/T/CC), hypodense compared with the liver parenchima, heterogenous and of low density on pre-contrast imaging, with progressive enhancement after contrast administration and mass effect on the adjacent kidney and right hepatic lobe; also, a similar lesion on the left adrenal gland of 61/45/60 mm and a right inguinal lymph node (27 mm). Hormonal assessments showed no secretion; congenital adrenal hyperplasia and adrenal insufficiency (giving the distruction of the cortex of both glands) were also ruled out. There was a rapid increase in inguinal lymph node size, so an excisional biopsy was made; the morphologic and immunohistochemical characteristics revealed lymph node metastasis of malignant melanoma (S100 intense positive in nucleus and cytoplasm, HMB45 intense positive in cytoplasm of tumoral cells). The patient was directed to Oncology Department and lost to follow-up.
Discussion
Adrenal metastasis are the most common malignant lesions involving the adrenal gland. On the other hand, bilateral adrenal masses due to melanoma metastasis are rare, usually nonsecretory, associated with short-term survival, being uncommon for metastatic cancer to appear in the adrenal gland before the primary lesion is known.

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EP47

Normotensive primary aldosteronism in a young woman taking minipill – case report

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Background
Primary aldosteronism (PA) is the most frequent cause of hormonal hypertension, typically associated with hypokalaemia. Whereas hypertension with no hypokalaemia can be present in even half of cases, hypokaleamia in normotensive patients is a very rare finding. Mechanisms that act against developing hypertension despite aldosterone excess are at least a few. Some patients with previous low blood pressure increase its values because of hyperaldosteronism, thus still maintaining them in the upper part of the normal range. When screening patients with normotension, other than antihypertensive drugs can interfere with renin–angiotensin–aldosterone system and thus alter biochemical results, with oral anticontraceptives amongst them.
Case description
34-year-old female, more than a year postpartum, was referred to Endocrinology Department because of refractory hypokalaemia of unknown origin. Kalium concentrations as low as 2.8 mmol/l were observed. Her blood pressure was within the normal range. Because of her gastric disturbances, she had her abdomen CT already performed and left adrenal incidentaloma of 15×20 mm in diameter and density of (–)20 Hounsfield Units was found. She was taking oral contraceptive minipill – desogestrel. Serum aldosterone and direct renin measurements were 11.5 ng/dl and 2.86 μIU/ml [AARR = 4.02 (cut-off level <3.7)], pointing to the possibility of primary aldosteronism. After 6 weeks of withdrawal of desogestrel, repeated screening and saline infusion test results were consistent with PA diagnosis. To assess lateralization of aldosterone production the patient underwent norcholesterol scintigraphy, because of poor availability of adrenal venous sampling and our good experience. Although the image was non-specific, the patient underwent left adrenalectomy without additional testing. Serum aldosterone, direct renin levels and kalaemia returned to normal.
Conclusions
Even in the absence of hypertension, isolated hypokalaemia itself should prompt screening for autonomous aldosterone secretion. In women of reproductive age, progestin-containing drugs can alter other hormone levels and that should be taken into account if biochemical testing is performed.

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EP48

Clinical case of Takotsubo syndrome after adrenalectomy

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Introduction
Described in 1990 by N Sato *et al*., Takotsubo syndrome (TS) is an acute myocardial dysfunction with the development of heart failure.
Objective
We present a description of the clinical case of ST after adrenalectomy for pheochromocytoma.
Results
Pheochromocytoma of the left adrenal gland (methanephrine 553.7 pg/ml (norm <65) and plasma normmetanephrine 458 pg/ml (norm <196) was verified in 27-year-old patient L. with hypertensive crisis. In connection with severe hypotension associated with doxazosin, 6% hydroxyethyl starch was infused. At endoscopic adrenalectomy, a transient increase in blood pressure and heart rate was observed, after compression of the left adrenal vein – severe vasoplegia, signs of acute left ventricular failure with the development of alveolar pulmonary edema. The ventilation parameters were adjusted, the left adrenal gland was removed along with the tumor. On artificial pulmanory ventilation with 100% oxygen, infusion of norepinephrine and mesatone: BP 115/75 mmHg, heart rate 138/min, central venous pressure +23 cm water column, saturation 90%, leukocytosis 18.4×10^9/l, glycemia 13.4 mol/ , CK-MB 37 U/l, hsTnl 0.671 ng/ml (<0.016). ECG: subepicardial ischemia in the anteroseptal apical segment; LV echocardiography 36×57 mm, systolic gradient at the exit of the left ventricle 2.7 mmHg, ejection fraction of 30%, akinesis of the middle segments of the septum, anterior septum, anterior, lateral, posterior, lower walls of the LV, apical segments of the septum, anterior, lateral, lower walls of the LV; X-ray signs of cardiogenic edema of the right lung. The patient was diagnosed with: Takotsubo syndrome. Acute left ventricular failure, alveolar pulmonary edema. Cardiogenic shock. Acute renal injury. Treatment: Artificial pulmanory ventilation, norepinephrine and mesatone, clexane, iso-mik before stopping the clinical signs of pulmonary edema; in-blocker. After recovering consciousness, the patient was extubated, neurological deficit was absent, the therapy for acute renal injury was administrated. Subepicardial anterior widespread changes in the type of ischemia, deepening of the T wave in leads V2–V6, inversion of the T wave in III, aVF were observed on the ECG. The global systolic function of the LV was recovered, hypokinesis subsequently persisted in the apical segment. Against the background of anticoagulant therapy, in-blockers and ing-ACE, shortness of breath decreased and exercise tolerance was recovered.
Conclusion
When conducting an adrenalectomy, it is necessary to consider the possibility of developing stress-induced myocardial dysfunction.

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EP49

Ectopic ACTH syndrome presenting as pneumocystis pneumonia

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Ectopic adrenocorticotropic hormone (ACTH) syndrome occurs in about 5–10% of all patients with ACTH-dependent hypercortisolism. We present the case of a 35 year old gentleman who presented with a six month history of progressive 16 kg weight gain and breathlessness. Pulmonary imaging revealed bilateral infiltrates suspicious for Pneumocystis pneumonia (PCP). Physical examination was concerning for Cushing's syndrome, with facial plethora, easy bruisability and broad violaceous striae on his abdomen and thighs. Initial laboratory testing showed a profound hypokalemia (serum potassium 2.3 mmol/l (3.5–4.5 mmol/l). Endogenous hypercortisolaemia was confirmed with an overnight dexamethasone supression (ONDS) cortisol of 656 nmol/l. 24 h Urine Free Cortisol (UFC) was raised at 853 nmol/24 h. ACTH was elevated at 167 (72–63.3 pg/ml). The remainder of his pituitary profile was unremarkable with the exception of a testosterone of 3.0 (8.6–29 nmol/l). Ectopic ACTH was confirmed with Corticotroph Releasing Factor (CRF) testing failing to show a satisfactory rise in ACTH (147–175 pg/ml; 19%). Bilateral inferior petrosal sinus sampling (BIPSS) did not show a peripheral ACTH gradient and magnetic resonance imaging (MRI) pituitary was negative for an adenoma. Computed tomography of the thorax, abdomen and pelvis (CT-TAP) and Octreotide scintigraphy did not identify a culprit lesion. Calcitonin and urinary 5-Hydroxyindoleacetic acid (5-HIAA) levels were normal. His cortisol levels responded to Metyrapone with addition of Hydrocortisone to prevent adrenal insufficiency. His PCP was successfully treated with a course of co-trimoxazole. The clinical course was complicated by an admission with decompensation of congestive cardiac failure secondary to Cushing's cardiomyopathy. He is currently awaiting a 68Ga-DOTA-TATE PET/CT in the hope of localizing the ectopic ACTH-secreting tumour. This case highlights the profoundly immunocompromised state of severe Cushing's syndrome and the diagnostic challenge in localizing the offending lesion in ectopic ACTH.

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EP50

Adrenal hemangioma: Unusual case of adrenal incidentaloma

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Introduction
Adrenal hemangioma (AH) is a benign vascular tumor of the adrenal gland. The adrenal site of an hemangioma is extremely rare occurring only in 0.01% of cases and accounts for 63 reported cases in the literature. AH are often discovered as incidentalomas either by imaging studies or histologic examination. The role of computed tomography (CT) scan and Magnetic resonance imaging (MRI) is important for the differential diagnosis.
Case report
We report a case of a 56-year-old female patient who was referred to the department of endocrinology for exploration of an adrenal incidentaloma. The mass was detected at a CT scan performed to explore chronic back pain. The patient was treated for hypertension for 10 years. Clinically, she was suffering from headache, heart palpitations, sweating. Her blood pressure was high even though she was taking 2 antihypertensive drugs. She did not present any specific skin lesion. Multiple biological exams were performed: 24-h urinary catecholamine, 4 mg dexamethasone test, aldosteronin/renin ratio. The results were all negative. Since the tumor's radiological characteristic were leading to a malignant lesion, surgical treatment was decided and a right adrenalectomy was performed. The histological results concluded to an adrenal hemangioma. During follow-up, one year after the surgery, the patient continued to have a vague abdominal pain after, for which a CT scan was performed, showing a new mass in the left adrenal gland. The hormonal work-up was normal and the tumor was benign in the last CT scan. As for her family history, her sister was admitted for exploration of bilateral adrenal incidentaloma who turned out to be a benign non secretory adenoma.
Conclusion
The adrenal hemangioma is a rare adrenal gland lesion, benign and usually asymptomatic. Imagery is the best tool to characterize these silent adrenal masses. The main risks of the hemangioma are ignorance of malignancy, abdominal mass syndrome and bleeding. In this situation comes the role of Positron Emission Tomography with 18F-FDG to distinguish the malignant tumors and therefore reassure the proper treatment.

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EP51

ACTH-independent subclinical Cushing's syndrome secondary to primary bilateral macronodular adrenal hyperplasia

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Introduction
Primary bilateral macronodular adrenal hyperplasia (PBMAH) is an uncommon cause (<1%) of endogenous Cushing's syndrome (CS). Recently, due to increased number of incidental imaging findings of PBMAH, the clinical expression of the disease has changed in favor of oligosymptomatic or subclinical cases, compared to those with clinically manifest CS, or rarely with secretion of mineralocorticoids, or sex steroids.
Case report
A 51-year-old overweight woman was referred to our Institute for assessment of incidentally diagnosed bilateral macronodular adrenal hyperplasia. She had a history of dyslipidemia, and paroxysmal hypertension. Physical examination revealed no typical signs or symptoms of hormonal hypersecretion, except for a slightly elevated blood pressure (140/90 mmHg). Blood test results revealed normal plasma metanephrines, normmetanephrines, and normal renin aldosterone ratio. Subnormal suppression of serum cortisol following 1-mg overnight dexamethasone suppression test (2.34 µg/dl), 2×2 mg overnight dexamethasone supression test (1.92 µg/dl) and a suppressed ACTH (2.52 pg/ml) were suggestive of ACTH independent subclinical CS. Given that in PBMAH, adrenals may have aberrant receptors that stimulate excess cortisol secretion, we followed a screening protocol, which had positive (> 50% increase of serum cortisol) results for postural, mixed meal tests, and partially positive (> 25% increase of serum cortisol) for diphereline test. In our case, taking into account the patient's preference, as well as the mild clinical expression of the disease, we recommended active surveilling with yearly imaging and hormonal monitoring.
Conclusion
Considering the increased heterogeneity of PBMAH, due to modern imaging techniques that led to early detection, a clear diagnostic criteria is required in order to better characterize this entity and develop a tailored treatment plan.

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EP52

VHL-bilateral adrenalectomy with paragangliomas (A rare entity)

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Von Hippel–Lindau (VHL) disease, attributable to germline mutations in the VHL gene on the short arm of chromosome 3 (3p25-26) is an inherited condition which can give rise to paragangliomas. We present a case of 47 year old gentleman with bilateral pheochromocytomas in the past resulting in both adrenalectomies as a child in the 1980. His routine follow up subsequently picked up elevated urine Normetanephrines at 14.3 µmol/24 h 25 years postoperatively. His CT abdomen and pelvis revealed a 4.2 cm×2.8 cm mass between the IVC and right crus which was resected. His histology is reported as well-defined nests (Zellballen) bound by delicate fibrovascular stroma consistent with extra-adrenal paraganglioma. His urine metanephrines normalised post resection. He also had cryoablation to a left renal tumour in July 2008. In addition to a neuroendocrine tumour removed from the head of his pancreas in February 2009 through a Whipple's procedure which has left him diabetic. His most recent 24-h urinary metanephrines and fasting gut profile is normal. He is on hydrocortisone and fludrocortisone replacement which maintains his blood pressure around 120/80. He continues to be under annual follow up in our Joint Von Hippel–Lindau Clinic, endocrine clinic and genetics clinic aimed at early detection of any complications of his von Hippel–Lindau disease.
Conclusion
Paragangliomas are neuroendocrine tumours subdivided into parasympathetic and sympathetic paragangliomas with the formal localized to the head

and neck and the latter found in the thoracic, abdominal, or pelvic region. Clinicians treating VHL patients or having them under surveillance should be conscious about the existence of paragangliomas post adrenalectomy and be on the lookout for it post adrenalectomy.

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EP53

Delayed diagnosis of Cushing's syndrome

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Because of quite variable clinical manifestations of Cushing's syndrome and overlap with more common medical problems, its diagnosis is frequently mistaken, with consequent considerable delay from the first presentation to a different primary and secondary care physicians to a final diagnosis, often made by endocrinologist. The diagnostic latency in reported studies vary from six months to ten years. We report a case of a 54-years-old female admitted to the hospital through the emergency department because of prominent stiffness and persistent, sharp pain in lumbal spine and bilateral hip region, extreme fatigue, muscle weakness, easy bruising and poorly controlled hypertension. Also, she noticed weight gain and hirsutism. Because of mentioned disturbances present over the last three years, she had seen multiple specialists including cardiologist, neurologist and physiatrist but no further diagnostic procedures were recommended. Family history was strongly positive for cancer. On examination, she was plethoric, overweight (BMI 27.3 kg/m^2) with bruises in right gluteal region and both upper and lower extremities, proximal myopathy and blood pressure of 150/95 mmHg. Laboratory findings revealed sideropenic anemia (hemoglobin 82.8 g/l), blood glucose 5.77 mmol/l, hemoglobin A1c 5.39 %, normal electrolyte status and parameters of liver and kidney function. Hormonal examination showed ACTH of 1.3 pmol/l, morning cortisol 436.6 nmol/l with loss of diurnal variation, urinary free cortisol 303.6 nmol/l (12–486 nmol/l). Catecholamines, thyroid hormones, androgens, calcitonin and PTH were all in reference range; gonadotropins within menopausal levels. No significant supression of serum cortisol was achived after low-dose and high-dose dexamethasone supression tests (cortisol 582.9 nmol/l and 501.8 nmol/l respectively). A contrast-enhanced computed tomography and magnetic resonance imaging (MRI) of the abdomen demonstrated a 30 mm well-defined solid mass in the region of right adrenal gland. The diagnosis of Cushing syndrome was established and the patient underwent laparoscopic right adrenalectomy with patohistological finding of adrenal cortical adenoma. Based on postoperative hypocorticism and maintenance of subnormal cortisol levels, a substitution with Hydrocortison is initiated and continued in full replacement dose. Since the prevalence of Cushing's syndrome is increasing, raised clinical awareness among primary and secondary care physicians could lead to early referral of selected patients and timelier diagnosis with reduced rate of complications.

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EP54

Cortisol and androgens secreting left adrenal carcinoma

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Introduction

Adrenal carcinomas are rare tumor. It has an estimated incidence of ~0.5–2 new cases per million people per year. Just 25% of adults with hormone-secreting adrenal carcinomas present overproduction of both glucocorticoids and androgens. Women develop adrenal carcinomas more often than men.

Objectives

We report a case of 47-year-old female presented with weight gain, generalized weakness and hypertension for the last 6 months. Physical examination revealed central obesity, "moon facies" with facial plethora, facial hirsutism, and acne in the back of the chest, "bison neck", muscle weakness, hypertension and emotional lability.

Methods

The paraclinical examination showed: hypercholesterolemia, glucose intolerance, ACTH = 3.9 pg/ml (n = 5–65), 2300 h serumcortisol = 13.83 μg/dl, 0800 h serumcortisol = 25.2 μg/dl, urinaryfreecortisol (UFC) = 209.69 μg/24 h (n = 21–111), after 1 mg dexamethasoneovernight-supression – 0800 h serumcortisol = 16.63 μg/dl, testosterone = 1.14 ng/ml (n<0.75), DHEAS, plasma metanephrines and normetanephrines, aldosterone, renin are normal. Computed tomography examination showed left adrenal mass (11.5/7.7 cm) with blooming contour and hepatomegaly with subcapsular nodule on the right side.

Results

The left adrenal tumor was surgically excised by laparoscopic approach. Postoperatively the patient received hydrocortisone hemisuccinate substitution treatment with a favorable progression. Histopathological examination: adrenal carcinoma fully resected. Score Weiss = 6 points (high nuclear grade, mitotic rate 18/50 HPF, atypical mitosis, necrosis, sinusoidal invasion, capsular invasion). ENSAT stage II (T2N0M0). Postoperatively patient had secondary adrenal failure and received glucocorticoid substitution therapy; she loosed 9 kg, blood pressure and glucose levels returned to normal with no need for antihypertensive medication. She received local radiotherapy complicated with hepatic cytolysis and cholestasis (AST, ALT, GGT). 1 year postoperatively, computed tomography showed space replacing liver formation and normal right adrenal gland. She will start adrenolytic therapy with mitotane.

Conclusions

In adrenal carcinoma the prognosis was poor, but the use of adjuvant mitotane therapy increased over the 20-year time period, this improves recurrence-free and overall survival.

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EP55

Case of mineralocorticoid and androgen producing adenocortical carcinoma (ACC) and thyroid papillary microcarcinoma (MPTC)

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A 54-year-old female presented with muscle cramps and arterial hypertension. She was taking spironolactone 25 mg for hypertension. Her K+ level at first visit was 2.5 mmol/l. She was recommended to stop spironolactone, start potassium suplements, and measure Aldosterone, Renin, and K+ levels after 4 weeks. The Patient is a medical doctor. By her own decision CT of the abdomen was performed that showed 6.5 cm mass in left adrenal gland. The density was +28 HU. Some hypo-perfusion lesions were described in the liver. Full hormonal evaluation of the adrenal glands was performed. Metanephrines and cortisol were normal. Aldosterone – 25 ng/l (11.7–2236), Renin <1 ng/l (1.7–23.9), Aldosterone : Renin ration >25 (<20); It seemed tumor was secreting precursors of the aldosterone (deoxycorticosterone, corticosterone) and not the aldosterone itself. Testosterone – 0.66 (<0.41); Androstenedione – 5.6 (<0.82) 17(OH), Progesterone – 3.6 (<0.53); DHEA-Sulfate – 2.27 (0.5–5.5); At the same time patient was diagnosed with thyroid papillary microcarcinoma. She was advised to perform open surgery for adrenal mass and then thyroidectomy. However, she decided to undergo a simultaneous laparoscopic adrenalectomy and thyroidectomy with central prophylactic lymph node dissection. After surgery her potassium, adrenal androgens, renin, and aldosterone/renin ratio normalized. Postoperative MRI of the abdomen was unremarkable. On histologic examination, adrenal mass was 9×8×5 cm in size; Weiss score – 6; Ki67 – heterogeneous, up to 13% in hot spots. The thyroid nodule 0.5×0.4 cm – papillary carcinoma, follicular variant, sclerosing, infiltrative growth, with minimal ETE and focal lympho-vascular invasion. A total body 18F-FDG PET performed on 10/12/2019 was negative for pathologic uptakes. The stage of the ACC was defined as stage II, pT2pN0M0 low-to-intermediate risk of recur-

rence. The stage of PTC was defined as stage I, pT1apN0 M0, intermediate risk of recurrence, initial target TSH 0.1–0.5 IU/ml. Adjuvant therapy with mitotane and no RAI was recommended. Glucocorticoid replacement therapy (hydrocortisone 25 mg) was commenced simultaneously with mitotane treatment. The initial dose of mitotane was 500 mg uptitrated to 3000 mg. Mitotanemia measurement was recommended after 6–8 weeks from the initiation. Levothyroxine supressive therapy with 125 μg was prescribed. After 3 months TSH was fylly suppressed – 0.089, Tg – 0.5 (<0.2), anti-Tg <10 IU/ml. Neck US revealed a 5 mm round hypoechoic lymph node. Patient was recommended to adjust the dose of Levothyroxine to 112.5 μg and control of TSH, Tg, and Neck US in 2–3 months.

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EP56

Particular course of autoimmune polyglandular syndrome

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Introduction
Autoimmune polyglandular syndromes (APS) are affected by a primary lesion of 2 or more peripheral endocrine glands with the development of their insufficiency. Examination of people suffering from a disease, which may be part of combined autoimmune endocrinopathies.
The aim
To study the features of the course APS.
Materials and methods
Patient M., 11 years old with complaints of increased blood glucose, general weakness, thirst, dry mouth, dry skin, pain in the upper abdomen. Nausea, disturbed stool. Headache and dizziness. From the anamnesis: sick with type 1 diabetes for 5 years. Receives insulin therapy: NPX – 9+7 IU. Short acting – 3+3+31U. Laboratory and instrumental methods: GBA, GUA, A1C, ALT, AST, TTH, T4, cortisol, hepatitis B, C and Triglycerides.
Results
During laboratory and instrumental examinations were detected, subclinical hypothyroid and transaminase elevation. The results of laboratory studies: Hb Al c – 11.8, AST – 105 U/l, ALT 84 U/l, T4 free – 1.06 ng/dl, TTH – 7.12 mIU/l. Urinary cortisol 26.1 nmol/l, 26.8 nmol/l in blood.
Conclusion
Based on the data of anamnesis, physical examination, laboratory and instrumental studies, the following diagnosis – autoimmune polyglandular syndrome. In addition to insulin therapy, a cortef has been added to the treatment for chronic adrenal insufficiency, hepatoprotectors to eliminate the symptoms of autoimmune hepatitis.

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EP57

Primary adrenal lymphoma

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Primary adrenal lymphoma(PAL) is very rare and constitutes <1% of cases of extranodal lymphomas. Most common subtype of PAL is diffuse large B cell lymphoma. A 46-year-old male patient without any underlying disease was admitted to our hospital with a complaint of bilateral back pain, cough and fever. His laboratory tests revealed a hemoglobin: 5 g/dl (14–17.5), white blood cell: 3.8 10^3/μl (4.4–11.3), platelet: 111 10^3/μl (130–403). No pathological findings were detected in bone marrow biopsy. Abdominal MRI and chest CT revealed that bilateral adrenal mass without any lymphadenopathy. PET/CT showed a mass of 73×53 mm on the left adrenal gland and a mass of 145×90 mm on the right adrenal gland. Adrenal function was evaluated as non-functional adrenal mass. Surgical right adrenalectomy was performed. Postoperative basal cortisol level: 12.25 μg/dl (6.02–18.4), adrenal insufficiency is not detected. Histopathological examinationreported as diffuse large B cell lymphoma. R-CHOP chemotherapy was planned by consulting hematology. The 5-year cancer spesific survival rate for primary adrenal lymphoma is 38% and it should be considered as the differential diagnosis of the adrenal mass, especially when they are bilateral and grow rapidly.

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EP58

Challenges in pheochromocytoma diagnosis

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Background
The clinical diagnosis of pheochromocytoma requires improved clinical reasoning due to the scarcity of symptoms and complementary tests that are not always confirmatory.
Clinical case
A 58-year-old female patient sought an endocrinology service at the University Hospital for investigation of Adrenal tumor on the right, measuring 3.8×4.5×3.8 cm, discovered during routine ultrasound. He reported vague symptoms of abdominal discomfort and had been using irregular metropolol for more than ten years, due to mild hypertension and rare palpitations. Serial laboratory studies were carried out for Adrenal Incidentaloma which showed a only slight increase in Urinary Normetanephrines (1.2 ULN). No other evidence of hormonal excess was detected. During the entire clinical investigation, with suspension of antihypertensive medication for hormonal evaluation, the patient remained asymptomatic. Clinically, there was no evidence of pheochromocytoma. He was followed up on an outpatient basis for two years with urine metanephrine levels and image monitoring. The case was discussed in a clinical session with a radiology service and the characteristics suggested as the most likely hypothesis Adrenal Hemangioma, the tumor was lobulated, defined limits, hypodense and with peripheral calcifications, with heterogeneous contrast enhancement initiated in the arterial phase, and with a tendency to homogenization in the portal and late phases. Absolute wash out 37 and relative wash out 33. After two years of follow-up, she presented paroxysmal atrial fibrillation, and amiodarone was started. Service without availability of plasma metanephrines. PET-CT-FDG was performed detecting an Adrenal nodular lesion on the right, measuring 4×3.9 cm, indicating neuroendocrine tumor and whole body scintigraphy with MIBG-SPECT CT with nodular uptake in the right adrenal. The patient underwent a right adrenalectomy after preparation with alpha adrenergic block. She underwent major bleeding in the liver bed and hypovolemic shock. After surgery, the patient remained hemodynamically stable. Immunohistochemistry study confirmed the diagnosis of pheochromocytoma.
Conclusion
The diagnosis of pheochromocytoma requires clinical skill and the use of several diagnostic resources that, combined, help to clarify the clinical situation.
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Bone and Calcium

EP59

Extremely rare and slow-progressive parathyroid carcinoma: Case report

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Introduction
Parathyroid carcinoma (PC) is an extremely rare, aggressive and life-threatening form of primary hyperparathyroidism (pHPT). PC accounts for less than 1% of cases of pHPT, predominantly diagnosed in the fifth or sixth decades of life. Most parathyroid carcinomas are diagnosed after surgery.
Case description
A 51-year old man was admitted to the Hospital of Lithuanian University of Health Sciences, Kaunas clinics due to leg pain and general weakness. It is known from the medical history that kidney stones were observed in 2008. Ten years later hypercalcemia and chronic kidney disease (GFR – 12.6 ml/min per 1.73 m^2 (90–120)) was confirmed.

Laboratory tests
Hypercalcemia (Ca – 2.91 mmol/l (normal range 2.15–2.50), normophosphataemia (*P* – 1.25 mmol/l (0.81–1.45), ↑ uremic measurements (creatinine – 423 μmol/l (62-106), urea – 18.30 mmol/l (1.8–8.3), anaemia (Hb – 114 g/l (130–160), significantly ↑ PTH – 260.6 pmol/l (1.26–6.74), thyroid function was normal. Ultrasound investigation of the thyroid revealed normal echogenicity, homogeneous thyroid parenchyma and heterogeneous hypoechoic focal area with micro and macrocalcifications under the right lobe. US of abdominal cavity revealed the signs of nephrocalcinosis. Spine and pelvic X-ray revealed an old compression fracture of the Th-9 vertebral body and old fracture of the right iliac wing. DXA– osteoporosis: T-score –3.0 in the spine. The diagnosis of the parathyroid adenoma was denied after performing the parathyroid scintigraphy. Conservative treatment of hypercalcemia was performed with infusion therapy. The right inferior parathyroidectomy and right thyroid lobectomy was performed. The size of the parathyroid tumour was 4.5×4×3.5 cm, the weight of the specimen- 31 g. Histologically: carcinoma of the parathyroid gland pT1 LVi1. Tumour cell mitosis was monitored (5 mitosis/10 DPRL). Ki67 proliferation index was positive up to 5% of the cells. The MEN syndrome was denied, no mutation found. No metastasis of the tumour was observed. Persistent hypocalcaemia and hungry bone syndrome lasted for about a month after the surgery. Normocalcemia was achieved after the long-term treatment with alfacalcidol and calcium carbonate. The patient came to the endocrinologists for medical check-up after one year. Renal replacement therapy with an increasing need for dialysis was started. No recurrence of parathyroid tumour was observed. Ca–P homeostasis were in normal ranges.
Conclusion
Due to lack of local symptoms and slow progression this disease is often underdiagnosed. In most of the cases the PC diagnosis is confirmed by accidental removal of the parathyroid gland or after the manifestation of multiple chronic hypercalcaemia complications.

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EP60

GNAS mutation and affection of the endocrine system and bone: An analysis of 3 clinical cases

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Introduction
Activating and inactivating mutations of the GNAS gene (encoding the Gsα protein) cause McCune–Albright Syndrome and Albright's Hereditary Osteodystrophy, respectively. In both, the bone and the endocrine system are often affected. In McCune–Albright Syndrome the most common endocrine manifestation is precocious puberty, but thyroid lesions and hormonal overproduction are also described. In Albright's Hereditary Osteodystrophy there may be obesity, pseudohypoparathyroidism and other hormonal resistance.
Results (cases presentation)
Case 1: 20-year-old female patient, with McCune–Albright Syndrome. Followed in endocrinology appointments with subclinical hyperthyroidism, increased prolactin and GH/IGF-1. Currently 1.51 m, 59.2 kg, body mass index (BMI) 25.9 kg/m^2; prolactin 8.7 ng/ml (5.2–26.5) under bromocriptine; GH 7.3 μg/l (<1) and IGF-1 568 ng/ml (116–358) without therapy, having recently started lanreotide. Past medical history (PMH): Diagnosis at 2 years of age in the context of *café au lait* spots, stature acceleration, early peripheral puberty and bone dysplasia. During follow-up, she presented: elevation of GH/IGF-1 and growth >97 percentil (under sandostatin from age 10–15); hyperprolactinemia/galactorrhea (under bromocriptine from the age of 14); menstrual irregularities under combined oral contraceptive pills from age 11–19.
Case 2: 19 year-old, male patient, carrier of a GNAS mutation with suspected Albright's Hereditary Osteodystrophy. Followed in endocrinology appointments with TSH resistance hypothyroidism, currently with normal thyroid function under levothyroxine; short stature (1.43 m); normal/slightly elevated parathormone with calcium, phosphate and magnesium in the normal reference range; without other hormonal abnormalities.
PMH: primary hypothyroidism since the first year of life; genetic diagnosis performed at age 14 in the context of short stature, round face, brachydactyly and delayed psychomotor development.
Case 3: Female sex, 24 years-old with Albright's Hereditary Osteodystrophy. Followed in endocrinology appointments, currently presenting: overweight (body mass index of 28 kg/m^2), dyslipidemia and pre-diabetes (A1C 5.7%); slight elevation in parathormone 79 pg/ml (9–72) with calcium, phosphate and magnesium within the reference range and slight vitamin D deficiency; goiter with normal thyroid function; magnetic resonance with pineal cyst. Current medication: vitamin complex.
PMH: Genetic diagnosis of AHO at 12 years of age due to global developmental retardation, obesity and shortening of the 4th and 5th metatarsals and 4th metacarpals; self-injurious behaviours.
Discussion
Mutations with opposite effect on the same gene give rise to McCune–Albright Syndrome and Albright's Hereditary Osteodystrophy. Both affect the endocrine and skeletal systems differently. Due to the rarity and diversity of manifestations, they require multidisciplinary monitoring throughout life.

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EP61

A case of primary hyperparathyroidism presenting with acute pancreatitis

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A 42 year old male patient was admitted to the gastroenterology unit in due to severe abdominal pain and vomiting. He denied any chronic illness and drug usage. His family history was nonsignificant for any endocrine disease. Based on biochemical studies (lipase 2280 U/l, calcium 15.0 mg/dl, phosphorus 1.7 mg/dl amylase 631 U/l, creatinine 1.16 mg/dl, ALP 735 U/l) severe hypercalcemia induced acute pancreatitis was the diagnosis. 25 OH vitamin D was 5 ng/ml and parathyroid hormone level was 2496 pg/ml, Electrolytes, liver function tests, billlirubin, CBC differential, lipid profile, Calcitonin, and TSH level were in the normal range. A left-sided atypical mass (10 mm; 17 HU on non-contrast series, 45 HU on early and 82 HU on delayed contrast enhanced series) and renal stones were detected on abdominal CT. Mild osteopenia was evident on DEXA. Neck ultrasound revealed a heterogenous hypoechoic mass with increased vascularity and measuring 34×20 mm in size in the right parathyroid lodge. Calcium level normalized after zoledronic acid administration. Calcitonin was unavailable. When diagnostic work-up was underway, severe hypercalcemia ensued again. It could not be controlled with hydration and 160 mg/day furosemide, so a second dose of zoledronic acid was administered. Mildly elevated (<x1.5 UNL) urinary catecholamine levels in 7.5 l 24 h urine was at first attributed to polyuria. Polyuria was resulted from nephrogenic diabetes insipidus induced by hypercalcemia, hydration, and forced diuresis. However since an atypical adrenal mass was present and severe hypercalcemia ensued shortly after zoledronic acid therapy, we could not spend any time for repeating catecholamine tests or performing scintigraphy such as DOTATE/MIBG. Such a small lesion (10 mm) might have been invisible on scintigraphy. We diagnosed pheochromocytoma unless proven otherwise and alpha blocker therapy was commenced. The patient underwent parathyroidectomy and unilateral adrenalectomy at the same session without any peri- and post-operative complication. Following parathyroidectomy, calcium and parathyroid hormone reached a nadir of 7.5 mg/dl and 14 pg/ml, respectively (albumin 3.6 g/dl, phosphorus 2.2 mg/dl, magnesium 1.5 mg/dl). The final pathological report whether the adrenal lesion was a pheochromocytoma and the parathyroidal lesion was an atypical parathyroid adenoma or carcinoma are pending. Genetic tests for MEN are planned. Our case was challenging in terms of timing and decision of operation. Relatively young age and absence of any accompanying chronic disease probably helped to tackle potential complications including severe hypercalcemia, acute pancreatitits, and simultaneous extraction of adrenal mass and parathyroid adenoma.

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EP62

Resolution of severe primary hyperparathyroidism associated with classical skeletal complications following fine needle aspiration of suspected parathyroid adenoma

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Introduction
Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia, often caused by a single adenoma (85%) or four-gland hyperplasia (15%). Brown tumors are rare erosive bony lesions caused by localised rapid osteoclastic turnover resulting from hyperparathyroidism.
Case presentation
A 28-year-old lady presented to the Emergency Department with a 3-day history of fever, dry cough and generalized body aches. She reported sudden onset lower back pain radiating to her thighs and 1-month history of multiple joints pains predominantly knee joints. Biochemical investigations were consistent with PHPT: corrected calcium (cCa^2+) 3.20 mmol/l (2.23–2.50), phosphate 0.60 mmol/l (0.74–1.52) and PTH 160.3 pmol/l (1.6–6.9). Other relevant laboratory findings were: ALP 3259 U/l (40–150), 24 h urine calcium 4.75 g, normal renal and thyroid function. CT neck/chest revealed a right thyroid nodule measuring 2.5 cm and brown tumors on multiple ribs, cervico-thoracic spine and long bones. MRI spine also showed brown tumors in the right sacral alar and iliac bones. Sestamibi SPECT/CT was later performed indicating a possible hyperfunctioning parathyroid lesion on inferior pole of the right thyroid lobe. There was focal increased tracer uptake in the right iliac crest, left distal tibia and left elbow suggestive of brown tumors. Although referred for a parathyroidectomy, an ultrasound guided FNAC of the right thyroid nodule was performed prior to surgery at the request of the surgical team. FNAC findings were suggestive of parathyroid tissue. Following the procedure, the patient reported pain at the site of FNAC, and pins and needles in all limbs. On neck examination, there was a 4 cm right sided hard and tender neck lump. Laboratory tests revealed cCa^2+ 1.92 mmol/l and PTH 4.8 pmol/l. Neck ultrasound showed a 3.77×3.07 cm mixed echogenic nodule with cystic changes in the right thyroid lobe. She was treated for hungry bone syndrome requiring calcium and magnesium supplementation. Haemorrhage and apoplexy of the culprit parathyroid adenoma due to FNAC was suspected. Surgery was cancelled and she was discharged on calcium carbonate and calcitriol. At her last Endocrine clinic review, she was well and remained normocalcaemic (cCa^2+ was 2.14 mmol/l, phosphate 0.91 mmol/l) on calcium supplementation. She has not attended further endocrine follow-up thereafter.
Conclusion
Our patient with severe PHPT and significant bone disease appears to have resolution of PHPT following apoplexy of parathyroid adenoma secondary to FNAC. Spontaneous remission of PHPT due to necrosis and hemorrhage of a parathyroid adenoma, the so-called "parathyroid auto-infarction", "auto-parathyroidectomy" or "parathyroid apoplexy" is a very rare, but previously described phenomenon.

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An atypical presentation of a typical aetiology

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Introduction
Primary hyperparathyroidism (P-HPT) is a common endocrine disorder that occurs as result of adenomas (80–85%), hyperplasia (10–15%), atypical adenoma or carcinomas (<1%). Atypical parathyroid adenoma (APA) is a rare entity and represents intermediate group of parathyroid neoplasms of uncertain malignant potential with some atypical histological features.
Case details
We report a case of a 34-year male, with a background of hypertension (HTN) & chronic kidney disease (CKD), who was urgently referred by the GP to our hospital in view of alarmingly raised Calcium (Ca) & Parathyroid hormone (PTH). Clinical history revealed vague symptoms of ongoing lethargy. Bloods PTH 146 pmol/l (1.6–6.9), adjusted Ca 3.56 mmol/l (2.2–2.6). He was treated in the day unit with intravenous (IV) fluids and referred to our team who arranged for urgent admission as his calcium levels remained refractory to the mentioned intervention. Investigations revealed Vitamin D<20 nmol/l (>50), Alkaline Phosphatase (ALP) 66 IU/l (30–130), e-GFR 58 (>90). MEN workup including MR pituitary was normal.
Management
The patient initially recieved fluids following which intravenous(IV) Bisphosphonate was administered that dropped the Calcium to <3 over the next 48 h. He was arranged to have an urgent Sestamibi Nuclear Medicine Scan(NM SPECT CT) that revealed a 4.3 cm×6.5 cm×6.7 cm retrothyroidal mass in right lower neck with significant mass effect, displacing the thyroid and carotid sheath. Following this, he was urgently referred to the Surgical Team to have surgical intervention. Histopathology of the tissue samples revealed likely to be parathyroid adenoma with atypical features, most of which pursue a benign clinical course. Post operatively, Calcium has remained stable within normal limits on the follow up bloods since then. He is planned for Long term follow up in addition to regular clinical and radiological surveillance for features of malignancy or development of overt symptoms of MEN.
Discussion
Mutations in the CDC73 and HRPT2 gene are found in cases of parathyroid Carcinoma. In approximately one-third of affected individuals with changes in these genes, the mutation is inherited from a parent and is present in all of the body's cells. On the other hand, no specific Imunohistochemical signature has been identified for APA, thus rendering the diagnosis much more challenging. Patients with APA at diagnosis have a clinical and biochemical pattern much more severe than its benign counterpart, thus warranting the need for Urgent Medical and Surgical attention, followed by a long-term Management plan with MDT input.

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Malignant hypercalcemia – A rare case associated with abdominal liposarcoma

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Background
Malignant hypercalcemia (MH) occurs in up to 30% of patients who are diagnosed with cancery, being associated with later stages of the disease and poor prognosis. The physiopathological mechanisms responsible for MH are the production of parathyroid hormone-related peptide by the tumor (PTHrp) (80% of cases), osteolytic cytokine production (20%) and excess of $1,25(OH)_2$vitamin D production (1%).
Case report
We present the case of a 60-year-old man diagnosed, after an increase in scrotal and abdominal volume, with a 25 cm retroperitoneal mass suspicious for liposarcoma. Preoperatively, a hypercalcemia of 16.3 mg/dl was detected, with a serum phosphorous of 6.3 mg/dl and an acute renal failure. He was referred to our department and immediately started intensive fluid replacement, loop diuretics and glucocorticoids. From the initial investigation: PTH <3.0 pg/ml, 25(OH)vitamin D 18 ng/ml, alkaline phosphatase 91 UI/l, PTHrp<0.5 pmol/l and $1,25(OH)_2$vitamin D 224 pg/ml (18–71). He also did a bone scan scintigraphy that was negative for metastases and multiple myeloma was excluded. He was discharged from hospital but was again readmitted 15 days later with serum calcium of 19.2 mg/dl. Since bisphosphonate treatment was contraindicated, denosumab 120 mg was administered at day 1, 8, 15 and 29, with a good response (calcium of 11.5 mg/dl). After surgery, hypercalcemia completely resolved, with serum calcium levels between 8 and 9 mg/dl and normalization of $1,25(OH)_2$vitamin D (54 pg/ml).
Conclusion
Malignant hypercalcemia due to tumoral production of 1-alpha-hydroxylase with excess of conversion of 25(OH)vitamin D to $1,25(OH)_2$vitamin D is extremely rare. Most of the reported cases are associated with granulomatous diseases like sarcoidosis and, less frequently, with Hodgkin's Lymphoma or ovarian dysgerminoma. In summary, to the best of our knowledge, we report the first case of extrarenal production of $1,25(OH)_2$vitamin D associated to abdominal sarcoma in the literature.

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EP65

Differential clinical expression of primary hyperparathyroidism due to a parathyroid adenoma or hyperplasia

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Introduction
Primary hyperparathyroidism is nowadays frequently diagnosed due to routine blood calcium measured in the general biochemical profile. Primary hyperparathyroidism may be due to a parathyroid adenoma or parathyroid hyperplasia. Parathyroid adenoma may occur in the area of the parathyroid glands or may be ectopic.
Aim
The aim was to describe the differential clinical expression of primary hyperparathyroidism due to an adenoma or hyperplasia in a cohort of patients with the disease.
Methods
A cohort of 21 patient, aged 52–75 years old, 14 female and 7 male, suffering from primary hyperparathyroidism is described. Patients were diagnosed after diagnostic evaluation for various reasons which revealed an elevated blood calcium level. Subsequent evaluation revealed high PTH levels and the diagnosis of primary hyperparathyroidism was made. Further diagnostic evaluation to locate any hyperfunctioning parathyroid glands was made with neck ultrasound and scintigraphy with ^{99m}Tc-Sestamibi.
Results
In 19 of the patients a parathyroid adenoma was localized. In 17 of the cases it was in the area of the parathyroid glands, while in 2 of the patients it was in the upper mediastinum. In 2 of the patients, one male and one female the diagnostic evaluation did not reveal a parathyroid adenoma. In the cases with a parathyroid adenoma PTH levels were elevated, ranging from 121 pg/ml to 345 pg/ml. Calcium levels were also elevated, ranging from 10.8 to 13.5 mg/dl. In the cases, in which no parathyroid adenoma could not be localized, the diagnosis of parathyroid hyperplasia was made. PTH levels were only mildly elevated ranging from 75 to 88 pg/ml and calcium levels were also mildly elevated ranging from 10.6 to 10.9 mg/dl. One of the patients with the presumptive diagnosis of parathyroid hyperplasia decided to have surgery. One of the parathyroid glands was excised. The histology revealed parathyroid hyperplasia. The biochemical picture did not improve and conservative management was decided.
Conclusions
In conclusion, it appears that primary hyperparathyroidism due to a parathyroid adenoma is characterized by elevated levels of PTH and blood calcium in contradiction to parathyroid hyperplasia which is characterized by a milder clinical picture, PTH and calcium both mildly elevated. We propose that in the cases with a presumptive diagnosis of parathyroid hyperplasia, with a mild clinical picture, conservative management should be preferred along with careful follow-up.

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EP66

Fahr syndrome: About a case

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Introduction
Fahr syndrome is a rare disease, characterized by bilateral and symmetrical intracerebral calcifications, localized in the central gray nucleus and by the classic association with hypoparathyroidism. We report a case of Fahr syndrome associated with postoperative hypoparathyroidism.
Case report
A 58 year old female patient with a history of total thyroidectomy 18 years ago. She complained of chronic paresthesia, muscle cramps complicated sometimes by attacks of tetany mistaken for hysterical crisis. The evolution was marked last year by the installation of a state of generalized convulsive crisis. The assessment carried out in the emergency department objectified a deep hypocalcemia at 70 mg/l, a hyperphosphoremia, associated with a low serum level of PTH on radioimmunoassay (PTH=0.001 pg/ml). On the electrocardiogram the QT was lengthened. The cerebral scanner had shown bilateral and symmetrical calcifications of the central gray nucleus of the upper and sub tentorial stages. The diagnosis of Fahr syndrome secondary to hypoparathyroidism was accepted and the patient was substituted with calcium and vitamin D.
Discussion
Fahr syndrome can complicate untreated hypoparathyroidism at any age. The pathophysiological mechanisms of intracerebral calcifications are poorly understood. In front of phosphocalcic metabolism disorders, and specially in case of associated neuropsychiatric signs, intracerebral calcinosis should be sought. Treatment is based on the correction of disorders of phosphocalcic metabolism which often leads to a marked improvement. This observation illustrates the diagnostic difficulty with the clinical heterogeneity of this pathology and the advantage of systematic research of postoperative hypoparathyroidism in order to avoid its deleterious complications.
Conclusion
Fahr syndrome is a rare entity with contrast between a rich and severe symptomatology and a simple and effective treatment. The etiologies are dominated mainly by hypoparathyroidism.

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EP67

A peculiar case of primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia due to an unregulated overproduction of parathyroid hormone (PTH). PHPT is most commonly caused by a single adenoma of the parathyroid gland, usually located just behind the thyroid gland. However, in rare cases, they can have an ectopic location, including intrathyroid adenomas. In some cases, the measurement of intact PTH in the wash out fluid obtained by US-Fine Needle Aspiration (FNA) can be useful in clarifying the etiology of these lesions. Treatment of this condition usually consists of surgical removal of the adenoma.
Case report
A 48-year-old man with complaints of fatigue and malaise was diagnosed with PHPT (total serum calcium concentration, 12.4 mg/dl [reference range, 8.6–10.5 mg/dl]; PTH 462.1 pg/ml [reference range 12–67 pg/ml]) and referred to the Endocrinology department. He presented a background history of symptomatic renal stone disease. A neck ultrasound was performed and the only abnormal finding was a predominantly cystic right lobe thyroid nodule with 21 mm. The patient underwent US-guided FNA of the lesion. PTH measurement in FNA wash-out fluid was significantly elevated (PTH 7199 pg/ml). A week after the procedure he returned to our department reporting he felt neck pain following the procedure and has been noticing distal paraesthesias in the upper limbs. Blood test results showed significant hypocalcemia and supplementation with calcium and calcitriol was started. A 99 Tc-sestamibi scan was performed but did not reveal any abnormalities suggestive of parathyroid disease. An ultrasound reassessment showed a decrease in the thyroid nodule's size. The patient was closely monitored. Recurrence of hypercalcemia was later observed, nearly a month and a half after FNA. At the date of the last appointment, he was asymptomatic and was offered surgical treatment.
Discussion
We present a case of FNA induced transitory remission of PHPT in a patient with an intrathyroid parathyroid adenoma. We conjecture that intra-nodular hemorrhage might have occurred, which temporarily affected the viability of the autonomous parathyroid tissue. A few similar cases of spontaneous or induced remission of PHPT after FNA had been previously described in the literature. This remission can be transitory or permanent, depending on the degree of cellular damage, thus periodic follow-up of these patients is recommended.

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Shear wave elastography role in localizing secondary hyperparathyroidism

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Introduction
Secondary hyperparathyroidism (sHPT) is a prevailing complication of chronic kidney disease (CKD) caused by the disturbance of calcium,

phosphate, and vitamin D, with high concentrations of serum parathormone (PTH) leading to high rates of cardiovascular and bone disease. The incidence and prevalence of chronic kidney disease, including kidney failure requiring renal replacement therapies (RRT) is rising in Europe. The objective of this study is to determine using 2D shear wave elastography, the elastographic characteristics of hyperplastic parathyroid glands in patients with chronic kidney disease and determine whether the technique adds diagnostic and localization information of these glands.
Materials and methods
We evaluated patients with stage 5 CKD under hemodialysis therapy: clinical, 2B ultrasound, Power Doppler, and shear wave elastography with computer assisted quantitative measurement of tissue elasticity with high accuracy linear probe on Supersonic Aixplorer machine.
Results
We evaluated 59 patients (male to female ratio 27:32) with mean age of 56.95±10.92, mostly above 65 years old, with confirmed CKD stage 5, registered on ERSD (end-stage renal disease) program, on RRT (renal replacement therapy). A total number of 97 hyperplastic parathyroid glands were studied. Hyperplastic parathyroid glands appear as soft tissue, with a mean SWE value of 7.835±2.944 kPa and minimum value of 4.630±2.272 kPa and a maximum value of 12.956±6126 kPa. We compared the elasticity index of hyperplastic parathyroid glands with elasticity index of thyroid tissue (mean SWE=13.780±4.039) and found significant differences.
Conclusion
The aim of this prospective study was to quantify the value of 2D Shear Wave Elastography in localizing secondary hyperparathyroidism. Elastography can be a useful tool and can better differentiatiate on tissue elasticity when localizing parathyroid hyperplasia in secondary hyperparathyroidism.

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Coexisting primary hyperparathyroidism and plasma cell dyscrasias – A case series

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Introduction
Coexistence of primary hyperparathyroidism and plasma cell dyscrasias such as multiple myeloma and monoclonal gammopathy of uncertain significance (MGUS) is rare. This can cause diagnostic uncertainty regarding the aetiology and relative contribution of each disorder to hypercalcaemia. We present a series of five individuals with this combination.
Case series
All five patients were referred to the endocrine clinic with hypercalcaemia. The series consists of four women and one man with a median age at diagnosis of only 53.5 years (40–76). Presenting complaints included aches and pains at different sites and constipation (one case); one case had incidental hypercalcaemia. Median calcium level was high at 2.95 mmol/l (range 2.57–3.26; reference value 2.2–2.6 mmol/l), 25 hydroxy vitamin D: 32 nmol/l (range 19–67; reference value 50–150), Parathyroid hormone (PTH) levels: 12.77 pmol/l (range 6.2–18.7; reference value 1.9–6.8). Two patients had evidence of nephrocalcinosis and four had osteopenia on bone density scan (one patient had lytic lesions and no formal bone density assessment). Four patients had confirmed multiple myeloma simultaneously diagnosed with primary hyperparathyroidism, when investigated for hypercalcaemia. The other patient had MGUS. The patient with MGUS had negative ultrasound and radio-isotope scanning for parathyroid adenoma. Of the patients with multiple myeloma, three had localised parathyroid adenomas and two have been referred for surgery. Last patient with multiple myeloma and failed parathyroid adenoma localisation is on Cinacalcet, having declined further investigations or surgery.
Conclusion
Concomitant diagnosis of primary hyperparathyroidism and multiple myeloma is rare in the literature, even though the conditions represent common independent causes of hypercalcaemia. Median age at diagnosis was only 53 years and youngest patient with multiple myeloma was only 40 years, which is earlier than expected with either disorder. Median calcium at presentation was 2.95 mmol/l, which is higher than expected with either disorder. The diagnostic approach should always consider evaluation of the common causes of elevated calcium. A simple screening test inclusive of PTH levels, 25 hydroxy vitamin D, serum protein electrophoresis and either urinary Bence Jones protein or serum free light chains, at the first appointment, could give significant insights into the pathophysiological pathways of elevated Calcium.

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EP70

Rare cause of hypercalcemia: Parathyroid carcinoma

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Introduction
Primary hyperparathyroidism is usually caused by parathyroid adenoma or hyperplasia. Parathyroid carcinoma is a rare cause of hyperparathyroidism with a frequency ranged from 0.3 to 2.1%. Features that increase the likelihood of parathyroid carcinoma in patients with primary hyperparathyroidism are larger tumor size, symptomatic disease, marked hypercalcemia, and very high serum parathyroid hormone (PTH) concentrations. Preoperative localization studies do not reliably distinguish carcinoma from adenoma, so the diagnosis is typically made at the time of surgery.
Case report
Sixty-five-year-old asymptomatic patient with diabetes mellitus and arterial hypertension was referred to our outpatient clinic because of a chance discovery of hypercalcemia, with calcium 2.79 mmol/l (normal range 2.2–2.6 mmol/l), ionized-calcium 1.58 mmol/l (1.12–1.23 mmol/l) and intact parathyroid hormone (iPTH) 194 ng/l (10–65 ng/l). The patient underwent an ultrasonography of neck region and a subtraction thyroid scan. Investigations did not confirm any neck mass. We performed a choline PET CT that showed a larger cystic mass on the right side of thyroid gland, suspicious for parathyroid carcinoma. Before surgery he did CT scan of neck and thorax, which showed a large tumor (4×3×5 cm in size) of parathyroid gland, without distant metastases. The patient was referred to a thoracic surgeon. Histological findings of resected tumor confirmed a parathyroid carcinoma. His serum calcium and iPTH concentrations after surgery were normal (Ca 2.12 mmol/l, iPTH 30 ng/l).
Conclusion
Primary hyperparathyroidism is often recognized as a result of biochemical screening. The majority are asymptomatic patients with mildly elevated serum calcium concentrations. Although there is an overlap in the clinical in biochemical presentation of benign parathyroid disease and parathyroid cancer, there are some features that increase the likelihood of parathyroid cancer, one of them is tumor size. So even in asymptomatic patients, localization studies can help you to determine the right management and best decision for each individual case.

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Efficacy and safety of pamidronate in the treatment of parathyroid hormone-dependent hypercalcemia in hospitalized patients

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Background
Bisphosphonates are effective in malignancy-related hypercalcemia and have been beneficial in parathyroid-hormone (PTH)-dependent hypercalcemia in small randomized-controlled trials. However, data regarding efficacy and safety in PTH-dependent hypercalcemia is limited, and pamidronate is not indicated for this condition.
Objective
To evaluate efficacy and safety of pamidronate in moderate-severe PTH-dependent hypercalcemia. Control groups were patients with PTH-dependent hypercalcemia who did not receive pamidronate, and patients with PTH-independent hypercalcemia who received pamidronate.
Methods
Medical charts of patients hospitalized with hypercalcemia >12 mg/dl between 2014 and 2019 were reviewed. Cases were categorized as PTH-dependent or PTH-independent. Epidemiological and clinical characteristics, laboratory findings including albumin-corrected calcium, creatinine and phosphorus levels, and treatments were extracted. Patients with PTH-dependent hypercalcemia who received pamidronate were compared with similar patients who did not receive pamidronate, and with patients with PTH-independent hypercalcemia who received pamidronate.
Results
There were 37 hospitalizations in 34 patients with PTH-dependent hypercalcemia; pamidronate was given in 24 cases (64.8%). Calcium at admission was higher in the pamidronate-treated group than in the untreated group (mean 14.4 mg/dl vs 13.0 mg/dl, $P=0.001$); baseline creatinine and phosphorus levels were similar. Nadir post-treatment calcium was similar

between groups (10.9 mg/dl vs 11.4 mg/dl respectively, $P=0.247$), however the calcium delta was higher in the pamidronate-treated group (3.5 mg/dl vs 1.6 mg/dl, $P=0.003$). Of pamidronate-treated patients, none developed hypocalcemia or renal failure; nadir phosphorus was lower than in untreated patients (1.7 mg/dl vs 2.4 mg/dl, $P=0.005$). Sixteen patients underwent parathyroidectomy in the year following hospitalization. Regarding PTH-independent hypercalcemia, pamidronate was given to 60 patients in 67 hospitalizations; 64 cases were malignancy-related. Patients with PTH-independent hypercalcemia were older than their counterparts with PTH-dependent hypercalcemia (73.9 vs 62.4 years respectively, $P<0.001$). There were no between-group differences in calcium (14.8 mg/dl vs 14.4 mg/dl respectively, $P=0.278$) or creatinine at admission; the PTH-dependent group had lower phosphorus (2.48 mg/dl vs 3.54 mg/dl, $P<0.001$). Median pamidronate dose was 60 mg in both groups. Additional treatments included fluids (97.8%), furosemide (51.6%), calcitonin (45.1%) and cinacalcet (3.3%) with no between-group differences. Of PTH-independent cases, 36 (53.7%) received glucocorticoids; few received immediate oncological therapy. Following treatment, calcium fell by 4.48 mg/dl (PTH-independent) vs 3.51 mg/dl (PTH-dependent), $P=0.048$ and by >2 mg/dl in 53 (82.8%) vs 18 (75%) respectively, $P=0.408$. Forty-eight patients in the PTH-independent group and 2 in the PTH-dependent group died within 1 year.

Conclusion

The efficacy of pamidronate was similar in PTH-dependent and PTH-independent hypercalcemia, with no significant documented side-effects in the PTH-dependent group. Pamidronate should be considered part of the treatment arsenal in moderate-severe PTH-dependent hypercalcemia.

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EP72

Hypophosphatemia: Collateral damage in parenteral iron administration

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Introduction

Iron-induced hypophosphatemia is a well-known adverse effect in patients receiving parenteral iron supplementation. Initially thought to be transient and mild, it seems that in certain cases, especially in patients who require repeated intravenous iron administrations, it can lead to spectacular symptomatology and serious complications.

Case report

A female patient, aged 61 was referred for intense muscle and bone pain, severe impaired mobility, vertigo and headaches. She has been known with Rendu–Osler syndrome which led to recurrent severe epistaxis and anemia requiring repeated administrations of intravenous ferric carboximaltose for the last 2 years. Laboratory results revealed severe hypophosphatemia (0.49 mmol/l) with hyperphosphaturia (Tmp/GFR 0.21 mmol/l) and an elevated FGF23 level (137 pg/ml). Two months before presentation, the patient was also diagnosed with vitamin D deficiency and secondary hyperparathyroidism (25 OH vitamin D 7 µg/l, PTH 114 ng/l, corrected calcium 2.01 mg/dl) which further increased phosphate renal leak. The correction of hypophosphatemia in this case was achieved after changing the parenteral formula from ferric carboximaltose to saccharated ferric oxide, oral phosphate and vitamin D supplementation confirming the literature according to which a greater risk for hypophosphatemia is associated with ferric carboximaltose through an increase of FGF23.

Discussion

Beyond the major impact on patient's quality of life, chronic and severe hypophosphatemia may lead to other serious complications such as hemolytic anemia, osteomalacia and fragility bone fractures, cardiac and pulmonary dysfunctions, delirium, seizures and coma. The mechanism in this situation seems to be a decrease in phosphate renal reabsorption and inhibition of renal 1-alpha hydroxylation due to an increase in FGF23 level, which is reported to reach a maximum in the first week after parenteral iron administration. Apparently, the risk of phosphate depletion is related to several risk factors like iron formulation, frequency of administration, renal function, previous vitamin D deficiency or hyperparathyroidism.

Conclusion

Hypophosphatemia should be sought in patients with recurrent parenteral iron administration, with monitoring of phosphate levels during 2–6 weeks after the iron administration. In addition, in order to avoid hypophosphatemia, it seems preferable to use an iron formulation devoid of ferric carboximaltose.

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EP73

Vitamin D revisited: Individualized Vitamin D normal values according to PTH levels; incidence and treatment of Normocalcemic Hyperparathyroidism in children

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Background

Childhood and adolescence are critical periods for the establishment of lifelong bone health. While most studies focus on vitamin-D regardless of PTH levels, Normocalcemic Primary Hyperparathyroidism (NPHPT) has been recognized more than 15 years ago as a variant of primary hyperparathyroidism (PHPT), characterized by persistently elevated PTH with normal albumin-adjusted total and ionized calcium, in the absence of secondary causes of hyperparathyroidism. PPHPT is related to an increased risk in development of osteopenia/osteoporosis, of parathyroid adenoma (15%) and hypercalcemia–hypercalciuria with renal consequences.

Aim

To redefine individual Vitamin-D sufficiency according to PTH levels, identify and treat biochemical disorders of PTH in normocalcemic children.

Methods

We performed a complete calcium metabolism evaluation (Ca, P, ALP, 25OHD, intact PTH) in all patients that visited our pediatric endocrine unit for 2 years (1 Nov 2016 until 31 Oct 2018).

Results and interventions

A total of 3060 patients – excluding those that consulted for vitamin D deficiency, Ca metabolism abnormalities or known renal pathology (i.e. Bartter syndrome). 154 patients (5.1%) had hyperparathyroidism: PTH >45 pg/ml (Horm Res Paediatr 2015;84:124–129) and normal total serum calcium levels: 51% were vitamin D replete (>30 ng/ml, group-1) and 49 % were deficient (<30 ng/ml, group-2). All received cholecalciferol (8000–16 000 IU/d)+calcium 1000 mg/day p.o. with a 3 m follow-up. In 6 patients (4 from group-1 and 2 from group-2) elevated PTH did not respond to 6 m of combined cholecalciferol/calcium therapy. These were switched to the non-calcemic synthetic 1-25(OH)2 vitamin-D analogue, paricalcitol 2 µg×1–3/day. Intact PTH (15–65 pg/ml) normalized (<35) in 5 patients by 3 m and in 1 by 10 m, with calcium in serum and urine (Ca/Cr 2-h morning sample) being normal.

Discussion

The incidence of NPHPT in childhood is high. In all normocalcemic children checked for vitamin-D, concomitant measurement of PTH is required, to individually define vitamin-D sufficiency for the given patient. Most of the cases seem to be secondary hyperparathyroidism as they are resolved with administration of cholecalciferol and calcium. Even in cases with vitamin D sufficiency, PTH fell to normal after administration of cholecalciferol and calcium.

Conclusions

Vitamin D sufficiency may not be for everybody a level >30 or 20 ng/ml, calcium intake playing also a crucial role. Subclinical Hyperparathyroidism is successfully treated with cholecalciferol (8000–16 000 IU/day)+calcium supplementation (1000 mg/day) in most cases. The non-responsive cases seem to be either primary or tertiary Hyperparathyroidism responding to Paricalcitol administration 2–6 µg/day, protecting bone and general health.

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EP74

Clinical case: Complicated differential diagnosis between postsurgical and functional hypoparathyroidism.

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Objective

Postsurgical hypoparathyroidism (HypoPT) is the most common etiology of disease and often occurs after thyroid surgery. However, the differential diagnosis between different forms of HypoPT in some cases remains a challenge. We present the clinical case of postsurgical and functional HypoPT combination.

Case description

A 44-year-old female was referred to the Endocrinology Research Centre. She underwent total thyroidectomy for follicular adenoma performed in

2009. Hypoparathyroidism developed after surgery, so calcium carbonate 1000 mg/day and calcitriol 0.5–1 μg/day were prescribed. She continued this therapy for 2 years and then stopped in 2011. There were no clinical symptoms of hypocalcemia. Laboratory tests revealed albumin-corrected calcium level within 2.11–2.25 mmol/l (normal value 2.1–2.55) and PTH 16.7 pg/ml (15–65). Since 2019 her condition deteriorated with seizures, muscle cramps and paresthesia recurrence. She also had a history of stomach ulcer and therapy with proton pomp inhibitors over last months. Laboratory examination showed a decrease of PTH level less 3.0 pg/ml, hypocalcaemia (1.8 mmol/l), hyperphosphatemia (1.9 mmol/l (0.74–1.52) as well as hypomagnesemia 0.6 mmol/l (0.7–1.05). 25(OH)D blood test was normal – 37 ng/ml (30–100). Calcium carbonate 1000 mg/day and calcitriol 1 mcg/day were immediately prescribed. Also she was started on magnesium supplements about 400–600 mg/day per os to control the hypomagnesaemia. After 6 months, lab. Test revealed normal magnesium (0.83 mmol/l), target calcium levels (2.32 mmol/l) and increased PTH to 24 pg/ml. There was complete symptom resolution. Step-by step the doses of calcium carbonate and calcitriol were reduced. Patient is currently receiving cholecalciferol in daily dose of 2000 IU. Her physical and laboratory examination remain normal.
Conclusion
Hypomagnesemia is recognized as a cause of hypoparathyroidism due to impaired parathyroid hormone secretion, with resultant hypocalcemia. This case demonstrates the importance of looking for all associated electrolyte abnormalities in patients with HypoPT.

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EP75

Vitamin D status and parathyroid hormone serum levels in women of reproductive age in Carpathian region

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Background
Vitamin D deficiency is a major public health problem in Ukraine. The aim of this cross-sectional study was to study the status of Vitamin D and parathyroid hormone (PTH) level in women of reproductive age in Carpathian region.
Materials and methods
A cross-sectional study was carried on a total of 416 nonpregnant and nonlactating women in the reproductive age group of 19–45 years during summer 2018. Demographic, socioeconomic class, and biochemical parameters for the estimation of serum 25(OH)D and PTH levels in women of reproductive age were studied. Serum 25(OH) D and PTH levels were estimated by chemiluminescent immunoassay (chemiluminescence) and colorimetric assay (Roche Cobas) technique.
Results
The mean age of individuals was 36±8 years. The median values for serum 25(OH) D and PTH level was found to be 17.42 (8–52) ng/ml and 57.2 (27.5–83.1) pg/ml accordingly. Vitamin D level less than 30 ng/ml was detected in 389 (93.5%) of participants. Vitamin D insufficiency was found in 148 persons (38.0%), deficiency – in 241 (62.0%). Significantly higher 25(OH)D level was registered in younger age group (19–34 years) as compared to 35–45 age group. In the univariable model, vitamin D deficiency showed a significant inverse association with age and body mass index. Serum PTH level was in the normal range in 345 (82.9%) of the subjects and high level – in 17.1%. Negative correlation between levels of 25(OH)D and PTH ($P=0.02$) was revealed.
Conclusions
There is a high prevalence of hypovitaminosis D among women of reproductive age. The risk of the development of osteoporosis and pregnancy-related complications in future is higher in these women.

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EP76

The importance of determining vitamin D epimers

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Vitamin D is a large group of structurally similar substances (calciferols) with diverse biological functions. Although approximately 40 different vitamin D metabolites have been determined so far, only 1,25-dihydroxyvitamin D was considered to be biologically active and the determination of 25-hydroxyvitamin D (25-OH D) served a tool to assess vitamin D supply. Recently it was found that also C3-epimers of vitamin D have their biological effect, however these effects differ from non-epimeric forms. The exact source of the epimers is not known but their proportion was found higher in mothers and newborns. The percentage of C3-epimers of the total 25-OH D range from 0% to approx. 60% for infants and from 0% to 45% for adults, respectively. Such a high percentage of epimers could lead to misclassification of vitamin D supply, as routinely used immunoanalytical methods are unable to distinguish epimers from non-epimeric forms of vitamin D and are burdened with the high proportion of cross-reactivity and interferences. Vitamin D assessment is a challenge mainly due to the low concentrations of analytes in blood, a large number of structurally similar metabolites and photo-instability of vitamin D molecules. Chromatographic separation of epimers combined with the mass spectrometry detection is recognized as the optimal method for the determination of vitamin D, however, in laboratory practice prevail immunochemical methods. In our study, we compared various methods and parameters associated with vitamin D in 80 serum samples. Surprisingly, the values of 25-OH D measured by chromatographic method and ELISA did not correlate together, but we found significant correlations between 25-OH D measured using chromatography and free 25-OH D. The choice of method is absolutely crucial when planning studies focused on vitamin D. Wide range of commercially available kits and at the same time, the unsatisfactory standardization of methods provides results that differ significantly from one another and can lead to problematic interpretation of the study outcomes. The work was supported by a grant of MH CZ – DRO (Institute of Endocrinology – EU, 00023761).

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EP77

Over-supplementation of vitamin D in a patient with unknown primary hyperparathyroidism

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Background
Primary hyperparathyroidism is more prevalent in women and sometimes the patients are without clinical signs. Parathyroid disorders aren't uncommon in the general population.
Clinical case
A woman 68-year-old was present to the ambulatory visit with multiple joint pains and generalized weakness, constipation and weigh loss since 1 year ago. She hadn't any history of fever, anorexia, nausea, vomiting or diarrhea. She refered that since 6 months she was taken a supplementation by her selves of Vitamin D (10 000 units of cholecalciferol) every day. No history of any chronic disease.
Lab results
We found a high values of 25(OH) Vitamin D 140 ng/ml, PTH 490 pg/ml and calcium values 16.6 mg/dl (8.5–10.1 mg/dl). The other results: Creatinine 0.8 mg/dl, GFR 58 ml/min, alkaline phosphatase 179 IU/l (46–119), urinary calcium 446 mg/24 h (42–353). Thyroid ultrasound: A solid cystic nodule in the right lobe of thyroid with dimensions 2.1×1.4×2.2 cm, without imaging evidence of a typical parathyroid adenoma. Parathyroid sestamibi scan: right parathyroid adenoma She was treated with intravenous (IV) saline and furosemide. The vitamin D3 was stopped and the patient underwent surgery, excision of the parathyroid adenoma. Pathological report confirmed diagnosis: parathyroid adenoma. The PTH values return to normal range after surgery and the calcium value was 10.2 mg/dl. In the following days calcium values were below normal range. Actually the patient was in treatment with calcium supplement and bisphosfonate for the treatment of osteoporosis. She was advice to have regulary follow up and to know sign of severe hypocalcemia.
Conclusions
Our case has a unknown primary hyperparathyroidism which was complicated with severe hypercalcemia as a result of over-supplementation with very high doses of vitamin D in a patient with unknown primary hyperparathyroidism.

Keywords: Primary hyperparathyroidism, hypercalcemia, vitamin D toxicity
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EP78

Hypercalcemic encephalopathy – A rare presenting manifestation of Sarcoidosis

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Background
Sarcoidosis is an inflammatory granulomatous multisystem disorder commonly presenting with noncaseating granulomas in lung and lymphoid tissue. Other organs like skin, eye and joints also involved.
Case report
We present a 62-year-old diabetic woman presented to the emergency with progressive alteration in sensorium and left hemiparesis for two days. Patient had lower respiratory tract associated with recurrent hypoglycaemic attacks two weeks back and resolved after a course of antibiotics. She had neck stiffness and left gaze deviation. Biochemistry revealed blood urea – 72 mg/dl, serum creatinine – 1.8 mg/dl, HbA1C – 6.7. Corrected calcium – 15.5 mg/d and phosphorous – 4.4 mg/dl. It suggested hypercalcaemia crisis with normal phosphorous levels. Further evaluation revealed Parathyroid hormone - 19.2 pg/ml and 25hydroxy vitamin D – 45.6 ng/ml levels which were normal. CSF analysis MRI brain serum immunoelectrophoresis which were normal ruled out meningitis, stroke and myeloma respectively. PET MRI whole body was done to rule out malignancy which revealed enhanced uptake in mediastinal lymph nodes. Sr ACE levels were elevated with 87 unit/l. Fibre optic Bronchoscopy was done and biopsy of lymph nodes revealed noncaseating granulomas. Biopsy was negative for acid fast bacilli and gene expert which ruled out tuberculosis. All the above investigations suggested sarcoidosis presenting as hypercalcaemia encephalopathy. Intravenous fluids to relieve dehydration and pamidronate 90 mg infusion was given to patient. Serum calcium levels settled down to normal gradually over two days to 10.2 mg/dl and sensorium improved. Patient was started on prednisolone 60 mg with tapering doses and monitored for next three months till steroids were stopped.
Discussion
Sarcoidosis usually presents with Hypercalcaemia as either renal failure or pancreatitis however encephalopathy is a rare manifestation. In our case encephalopathy with localising signs like left hemiparesis masqueraded as cerebrovascular stroke. Common causes of Hypercalcaemia include primary hyperparathyroidism, malignancy, milk alkali syndrome etc. Increased activity of 1 alpha hydroxylase enzyme in alveolar macrophages which converts 25 hydroxycholecalciferol into active form of 1,25 dihydroxycholecalciferol is the common cause of Hypercalcaemia in sarcoidosis. Other causes include increased production of parathyroid hormone related protein which, causes upregulation of 1 alpha hydroxylase.
Conclusion
Hypercalcemia can masquerade as stroke and should be evaluated when presented as metabolic encephalopathy with normal brain imaging. Sarcoidosis is a rare cause of hypercalcemic encephalopathy and is easily treatable when compared with primary hyperparathyroidism and malignancy related Hypercalcemia.

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EP79

Hypocalcemia due to pseudohypoparathyroidism diagnosed in adulthood

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Introduction
Pseudohypoparathyroidism (PHP) refers to a heterogeneous group of rare metabolic diseases, all characterized by end-organ resistance to the action of different hormones, primarily PTH. Main clinical characteristics are hypocalcemia and hyperphosphoremia associated with elevated parathyroid hormone (PTH) levels, frequently encompassing additional heterogeneous features, known as Albright's hereditary osteodystrophy. A molecular cause can be identified in 80–90% of patients with PHP. The most common underlying mechanisms are de novo or autosomal dominantly inherited genetic mutations within of GNAS. Most of these cases are diagnosed during childhood.
Case report
A 28-year-old male was referred by the general practitioner to study episodes of hypoglycaemia. Born in the Dominican Republic, he moved to Mallorca (Spain) at the age of 10. His medical record included active drug use (cannabis, cocaine, alcohol) and intellectual disability not clarified. He explained symptoms of weakness, dizziness and cramps in his legs since adolescence. The physical exam showed a peculiar phenotype: stocky body, rounded face, brachydactyly, obesity. A glucometer was delivered and no hypoglycemia was documented. The blood test showed normoglycemia, normomagnesemia, hypocalcemia, hyperphosphatemia, 25-OH-vitamin D levels slightly decreased and elevated levels of PTH. Calcium levels had not been carried out before. Based on these findings, a PHP was supposed and other tests were requested. CT scan showed basal ganglia calcification, HAND X-rays showed severe brachydactyly. DEXA scan revealed normal bone density. Hormonal blood test showed a subclinical hypothyroidism, low levels of IGF-1, normal testosterone and hypercalcitoninemia. An insulin-induced hypoglycemia test validated a growth hormone deficiency. The genetic study confirmed heterozygous mutation in the GNAS gene and the features are consistent with a PHP1A. Treatment was started with oral calcium and calcitriol.
Conclusions
It is important to diagnose, classify and properly treat hypocalcemia at an early age to avoid future complications. PHP requires, in most cases, a multidisciplinary approach with an endocrinologist to screen and treat the hormonal disorders.

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EP80

Role of vitamin D deficiency in comorbid disorders among the Chornobyl NPP accident survivors

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Endocrine comorbidity is a hot issue in radiation medicine featuring a concomitant radiation injury of several endocrine glands.
Objective
Establishing a link of vitamin D deficiency with thyroid and pancreatic disorders among the Chornobyl nuclear power plant (ChNPP) accident survivors.
Results
A blind sample ($n=60$) of subjects treated at the Radiation Endocrinology department in 2019 were selected for the study. Study sample included the ChNPP accident survivors (group 1, $n=40$) with 20 females (50%) and 20 males (50%) among them. The comparison group included patients (group 2, $n=20$) not exposed to radiation with 11 females (55%) and 9 males (45%) among them. Age of study subjects ranged from 37 to 75 years old (60.2 ± 9.8 years at an average). Failure of compensation of type 2 diabetes was the most common reason for hospital admission (48.3%), failure of compensation of hypothyroidism was in second place (46.7%). Incidence of the increased risk of vitamin D deficiency and excessive parathyroid hormone production in the Chernobyl accident survivors was somewhat higher than in non-exposed individuals, however with no significant difference (respectively 81.08% and 78.12%; $\chi=0.257$, $P=0.612$; 31.12% and 28.08%; $\chi=0.462$, $P=0.319$). Using a multivariate analysis the reliable model was obtained confirming the relationship of increased parathyroid hormone level and early subclinical signs of the target organs damage ($F=4.294$; $P=0.042$), which proves the feasibility of clinical questionnaires application. Reliable positive relationship was found between the vitamin D and free thyroxine levels ($r=0.729$; $P=0.001$) and negative one was found with the thyroid-stimulating hormone content ($r=-0.803$; $P=0.001$) in the ChNPP accident survivors, indicating a direct impact of vitamin D deficiency on the course of hypothyroidism. Decreased vitamin D concentration in the ChNPP accident survivors having got type 2 diabetes correlated with increased duration of metformin medication ($r=-0.421$; p=0.001) and body mass index ($r=-0.787$; $P=0.001$) indicating the need for correction of such insufficiency in the given contingent of patients. It was found that the parathyroid hormone level increases along

with the duration of type 2 diabetes and increase in creatinine clearance ($r=0.724$; $P=0.001$ and $r=0.799$; $P=0.001$).
Conclusions
Vitamin D deficiency has a negative effect on the course of comorbid disorders (type 2 diabetes and hypothyroidism) and excessive production of parathyroid hormone.

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EP81

Therapy of normocalcaemic primary hyperparathyroidism

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Normocalcaemic primary hyperparathyroidism (NPHPT) is becoming more common nowadays due to the increasing use of screening laboratory methods. In the care of the outpatient office of endocrinology of the 2nd Department of Internal Medicine, Faculty of Medicine, Masaryk University and St. Anne's University Hospital in Brno in the period between 1 January 2007 and 31 December 2019, there were a total of 304 patients diagnosed with primary hyperparathyroidism. At the time of diagnosis, 249 patients were normocalcaemic (serum calcium levels did not exceed 2.60 mmol/l) and 55 patients were hypercalcaemic. Any secondary causes of hyperparathyroidism were excluded. Two-thirds of patients were in their sixties and seventies at the time of NPHPT diagnosis. The high proportion of NPHPT patients can be explained by the relatively frequent examination of parathyroid hormone levels in normocalcaemia. Nearly one-fifth of all the studied patients with NPHPT had sustained or intermittent pathological increases in serum calcium within 10 years of the onset of the disease (47 patients). NPHPT can be considered a milder form of primary hyperparathyroidism or its initial form. Surgical treatment was recommended for all patients who showed marked hypercalcaemia and who had proven parathyroid adenomas. A similar practice was followed for normokalaemia patients if they also became overtly hypercalcaemic. Parathyroidectomies were also performed in five patients who remained normocalcaemic. In three of these cases, an adenoma was confirmed with MIBI scintigraphy. In two cases, thyroidectomies for nodular goitres were performed. An experienced surgeon performed a targeted search for the parathyroid adenomas in the course of the procedures and removed them after identification. In four cases, there was only a slight increase in calcaemia (up to 2.7 mmol/l) and long-term pharmacological treatment was indicated. Due to significantly reduced bone densities, bisphosphonates were administered. In one patient originally diagnosed with NPHPT, calcium serum levels increased to 3.13 mmol/l within one year of the onset of the disease. Parathyroidectomy was abandoned based on medical contraindication due to polymorbidity. Long-term treatment with cinacalcet was initiated and calcaemia decreased from 3.13 mmol/l to 2.60 mmol/l in four months. Normal calcium serum levels have been maintained for more than nine years.

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EP82

NCKX3 deficiency impairs to motor function and social behavior in mice

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Ca^{2}+ homeostasis has been reported to play important roles in various cell systems. In central nerves system, the dysregulation of Ca^{2}+ homeostasis can induce the excitotoxic and neurodegeneration. NCKX3 (Sodium/potassium/calcium exchanger 3), a novel member of the family of K+-dependent Na+/Ca^{2}+ exchangers, is an important component of intracellular Ca^{2}+ homeostasis. In addition, NCKX3 highly expressed in thalamic nuclei, in hippocampal CA1 neurons, and in layer IV of the cerebral cortex in the mouse brain. Here, we examined the effects of inactivation of NCKX3 in mice. NCKX3 deficient mice at 6 week-age were used for behavior assays. In comparison to wild-type (WT) mice, NCKX3 deficient mice displayed hyperactivity in the open field test. In addition, the rotarod test revealed motor learning defects in NCKX3 knock out (KO) mice. Moreover, NCKX3 deficient mice have reduced time spent on general sniffing, anogenital sniffing, and following behavior in social interaction test compared to WT mice. In three-chamber social ability test, NCKX3 deficient mice showed spent more time in the chamber contain un-familiar mouse. However, NCKX3 deficient mice exhibited significantly lower time spent in the novel mice in social novel test. NCKX3 deficient mice showed no change in cognition function in the novel object recognition and spatial learning in Morris water maze tests. These results indicated that NCKX3 mutation causes abnormal motor functions and social behaviors in mice.

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EP83

An unusual case of symptomatic hypercalcemia from Graves' disease in a young Filipino female

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Hypercalcemia in hyperthyroidism is usually asymptomatic, and related to a concurrent primary hyperparathyroidism. In this report, we describe a case of symptomatic hypercalcemia secondary to Graves' disease alone.
Case report
A 24-year-old Filipino female presented to the emergency department with generalized weakness, vomiting and abdominal pain. No other symptoms were noted. She was otherwise previously healthy. Family history was unremarkable. During physical exam, she was noted to have a non tender palpable thyroid gland without bruit. Her ECG showed sinus tachycardia. The complete blood count and electrolytes were normal however, ionized calcium was high at 1.6 mmol/l (NV 1–1.3). Renal function was normal. Hydration with saline and Furosemide 20 mg once daily was started though calcium levels remained elevated. Other causes of hypercalcemia were excluded as PTH was appropriate suppressed (8.8 ng/l; NV 14–72), vitamin D was also suppressed (15.29 nmol/LNV: >30). CT scan of chest and abdomen and bone scan did not point to any underlying malignancy nor metabolic bone disease. Medication history was also unremarkable. She was hyperthyroid with a suppressed thyroid stimulating hormone level of 0.004 pmol/l (NV:0.55–4.78), free T3 of >20 pmol/l (NV:2.3–4.2), free T4 of 8.4 pmol/l (NV:0.89–1.76). Thyroid receptor antibody levels were raised at 41.07 (NV:<1 kU/l). Supporting the diagnosis of Graves'disease. She was started on propylthiouracil 50 mg four times daily, along with propranolol 40 mg three times daily. She was subsequently seen after two weeks with normal repeat calcium level and thyroid function tests.
Conclusion
This report aims to highlight that thyroid disease should always be considered as a cause of hypercalcemia. A concomitant primary hyperparathyroidism should also be considered. The definitive treatment for the hypercalcemia is correction of thyroid function.

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EP84

A case of osteopetrosis/pycnodysostosis

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A 41 year old male patient presented to the endocrinology unit due to recurrent long bone fractures and teeth decay. His past medical history was nonsignificant for any chronic disease. He was a child of consanguineous marriage; his father and mother were first degree cousins. There were no other family members with similar phenotype or history of recurrent fractures He was 154 cm in height and weighed 58 kg. The arm span was 139 cm. Upper to lower segment ratio was 1.16. He had a beaky nose and frontal bossing. The nasopalatine canal was patent and incisive foramen were present as two seperate foramina. He had bilateral fractures of the mid-portion of the tibia cortex. He had normal puberty onset and secondary sexual development. He was not mentally retarded. He had abundant patchy yellow coloured mildly plaques over the torso, but he denied itching. We suspected cafe au lait spots. The dermatologist' initial diagnosis was tinea versicolor, however fungal hyphae was absent upon potassium hydroxide examination of skin scrapings. Hepatosplenomegaly, nephrocalcinosis, and nephrolithiasis was absent. He had bilateral optic nerve atrophy and left-sided hearing loss; however temporal CT, orbita MRI, and cerebral MRI revealed no obvious entrapment. Cerebral calcification was also missing. Optic coherance tomography was compatible with optic atrophy. Pattern-reversal visual evoked

potential revealed bilaterally (left side less than the right side) prolonged P100 latency. Sclerotic bones were evident on plain films of long bones of both upper and lower extremities, vertebrae, calvarium, and mandible. There was a fistula formation of left tooth root to the mandible but evidence of osteomyelitis was missing. High bone mineral density was detected on dual energy X ray absorptiometry (T score and Z score respectively for femur neck and lumbar vertebrae 1–4; +2.8, +3.4 and +6.8, +6.9). The laboratory data were as follows: ESR 19 mm/h (UNL 15 mm/h), CBC differential within normal limits, creatine kinase 69 U/l, LDH 232 U/l, reticulocyte 1.18% (UNL 3.00%), total bilirubin 0.26 mg/dl, ALT 13 U/l, AST 28 U/l, prothrombin time/INR 1.04, aPTT 31.6 sec, ALP 88 U/l, albumin 4.4 g/dl, phosphorus 3.8 mg/dl, glucose 89 mg/dl, total protein 7.5 g/dl, vitamin B12 144 pg/ml, creatinine 0.94 mg/dl, calcium 10.3 mg/dl, TSH 1.53 mU/l, 25 hydroxy vitamin D 15 ng/ml, parathyroid hormone 20 pg/ml. We think our case shares some features of mild-intermediate form of osteopetrosis and pycnodysostosis. Genetic testing has been planned and underway.

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EP85

Improvement of bone mass density in a pediatric patient with chronic kidney disease and growth failure

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Introduction
Multiple factors have been incriminated in growth retardation in patients with chronic kidney disease (CKD), such as metabolic acidosis, anemia, vitamin D deficiency with secondary hyperparathyroidism, under-nutrition, renal bone disease. The disease compromises vertical growth with up to one-third children having severe growth delay (below the third percentile for height). Optimal care and nutritional therapy alone, can't help the children with CKD reach their normal height without the supplemental growth hormone therapy.
Case report
An 11-year old male, known with chronic renal failure since birth, renal osteodistrophy with right renal transplant, came into our clinic for initiation of recombinant growth hormone(rGH) therapy. At the time, height was 126 cm (−3.32 DS), with a weight of 31 kg, in pubertal stage with bone age of 9 years. Predicted adult height was 165 cm, and midparental height was 180 cm. Metabolic bone parameters allowed us to initiate the rGH treatment. The additional question raised in that moment was related to the skeletal status: the patient had bilateral femoral neck fracture treated conservatively and in DXA whole body scan had a TBLH Z score of −3.84 which completed the diagnosis of osteoporosis. The patient had secondary hyperparathyroidism, in the context of CKD(GFR = 46.9 ml/min per 1.73 m^2) and previous chronic corticotherapy which recommended also byphosphonate(BF) initiation together with active vitamin D metabolites. We decided to postpone the BF therapy. Bone mass density reevaluation showed improvement under rGH treatment and 1-alpha-calcidol; thus after 1.5 years of rGH treatment, the TBLH Z score was −1.2 and without new fractures.
Conclusions
Despite not reaching the optimal height under rGH treatment period, we were able to improve bone mass density of the patient, which might be a certain benefit of it.

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EP86

Edentulism and the management of osteoporosis

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Complete or partial edentulism is common in middle age, especially in postmenopausal women. Edentulism may be the result of either dental problems or periodontitis or both. Periodontitis is characterized by systemic inflammation and may be accompanied by osteoporosis. Osteoporotic patients on treatment with anticatabolic agents may develop osteonecrosis of the jaw. The aim was to present the management of osteoporosis in an edentulous patient with severe periodontitis who developed multiple foci of osteonecrosis of the jaw. A patient, female aged 67, presented with osteoporosis, T score being −2.6 in the left hip. The patient also had severe periodontitis having already lost teeth in the maxilla. Anticatabolic treatment was administered. A year later the patient presented with severe dental problems and was completely edentulous. An extensive laboratory and clinical evaluation was performed. Osteoporosis improved and T score in the left hip was −2.4. Examination of the oral cavity revealed multiple foci of osteonecrosis of the jaw. Vitamin D and calcium were administered. Oral hygiene was taken care of and performed with the use of chlorhexidine solution. The patient was followed-up for a period of 6 months. Six months later examination of the oral cavity did not reveal foci of osteonecrosis. Thereafter, anticatabolic treatment was administered for the management of osteoporosis. In conclusion, management of osteoporosis in the edentulous patient presents unique problems. The patients are in the danger of developing osteonecrosis of the jaw. Additionally, dental implant installation may be impossible. Therefore, patients should be managed with caution. Oral examination should be performed in parallel with osteoporosis follow-up and oral hygiene should be taken care of.

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EP87

Is hip geometry modified in acromegalic patients?

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Introduction
Besides the amount of bone mineral assesed through bone mineral density (BMD), studies have shown that neck geometry parameters as hip axis length (HAL) and neck-shaft angle (NSA) could also be reliable parameters to be included in the hip fracture assesement. On the other hand, bone geometry is known to be modified in acromegaly in flat bones, thus hip fracture is not a recognized direct complication in acromegaly neither through bone mass or long bone geometry.
Objectives
The aim of the study is to evaluate hip axis length (HAL) and neck-shaft angle (NSA) in acromegaly compared with same parameters in non-acromegalic patients.
Methods
There were analyzed examinations of DXA of the proximal femur from 19 patients with acromegaly with a mean age of 59 years compared with the same number of examinations from 19 non-acromegalic patients with a mean age of 55 years. The data was collected from the authors database retrospectively. The independent Samples t-test was used to investigate the relationships between acromegaly and HAL and also NSA. Mean HAL value was significantly greater in acromegalic patients versus control group (116.1 mm vs 104.8 mm; $P<0.01$). Mean NSA in acromegalic group didn't show any significant difference compared with non-acromegalic patients (53.63 mm vs 54.84 mm).
Results
With the limitations of the small sample of patients, our study showed a significantly greater HAL in acromegalic patients, which has been associated with a higher hip fracture risk. Considering that no significant difference was found regarding NSA, our results support an increased hip fracture risk in acromegalic patients versus non-acromegalic patients based on a modified hip geometry inspite of known exposure at GH excess in adulthood only.

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EP88

Correlation of body mass index and bone mineral density in menopausal women

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Background /aim
Osteoporosis is a generalized bone disease, characterized by impaired bone firmness, resulting in an increased predisposition for fractures. In order to detect the subjects at risk for fractures, one should actively search for them, primarily in a group of postmenopausal women, considering clinical risk factors. Apart from others, the relevant risk factors are lack of estrogen and low body mass index (BMI <19 kg/m^2).: The aim of this study was to examine relationship between body mass index (BMI) and bone mineral density (BMD) in a group of postmenopausal women.
Methods
The study involved a group of 100 postmenopausal women, aged 46 to 70 years. (59.08±6.07). All subjects had their body mass and body height measured and BMI calculated. BMD was determined by DXA method (dual energy X-ray absorptiometry) by Lunar Prodigy Advance Unit. BMD was measured at central skeleton (lumbal spine and both hips). According to densitometry finding, the criterion for osteoporosis is T score less than –2.5 S.D. BMI values were correlated with total T score values of the lumbal spine and both hips, as well as total T score values of spine and hip.
Result
Results have shown that body mass was normal in 18% subjects, 1st grade obesity was found in 52%, 2nd grade obesity in 23%, 3rd grade obesity in 7% of subjects. Median BMI value was found in 28.27±4.12. Median lumbal spine T score was – 2.19 S.D.±1.25, and hip T score – 1.11 S.D.±0.95. A statistically significant positive correlation (r=0.01) was found between BMI and BMD of the hip, whereas between BMI and BMD of lumbal spine there was no statistically significant correlation. There was a statistically significant correlation (r=0.01) between BMD values of lumbal spine and hip.
Conclusion
BMI is a well known, significant predictor of BMD of entire skeleton. In postmenopausal women BMI is more important predictor of hip BMD, as compared to spine BMD. BMD of hip is increased with the increase of body mass and height in postmenopausal women due to considerable endocrine function of fat tissue which produces leptin and other bioactive peptides which have a protective role in bone structure. A lack of correlation between BMI and BMD of spine in postmenopausal women might be due to predominant effect of lack of estrogen and faster bone metabolism in spinal region (spongious bone).

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EP89

Cortisol secreting adrenal adenoma. A clinically silent cause of osteoporosis

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Adrenal adenomas are nowadays frequently diagnosed in the context of abdominal imaging. Osteoporosis may be a presenting manifestation of a cortisol producing adrenal adenoma. The aim was to present two cases of patients diagnosed and treated for osteoporosis who later in the course of the disease were diagnosed with a cortisol producing adrenal adenoma. Two patients, female aged 53 and 56 years, respectively, presented with osteoporosis. T score was −2.8 and −3.0 in the left hip, respectively. Bisphosphonates were administered. During follow-up the first patient developed gastritis and vague abdominal pain. An abdominal CT scan was performed which revealed an adrenal adenoma in the left adrenal gland measuring 1.8×2.6 cm. An extensive laboratory investigation revealed increased 24 h urinary cortisol levels, marginally decreased morning ACTH levels and normal morning cortisol levels. Cortisol levels were not suppressed after an overnight dexamethasone test. The diagnosis of a cortisol secreting adrenal adenoma was made. The second patient developed anemia during follow-up and an upper abdominal MRI was performed. The MRI revealed an adrenal adenoma measuring 1.2×1.8 cm. Laboratory evaluation revealed decreased morning ACTH levels, marginally increased urinary cortisol levels while morning cortisol levels were not suppressed after a low dose dexamethasone suppression test. Both patients did not have evidence of clinical Cushing's syndrome. Both patients were treated surgically for the adrenal adenoma. A year later laboratory evaluation revealed normal cortisol, urinary cortisol and morning ACTH levels. Osteoporosis improved after the excision of the adrenal adenoma. Bisphosphonates were discontinued. In conclusion, cortisol secreting adrenal adenomas may be a silent cause of osteoporosis. Osteoporosis resolves after surgical treatment of the adrenal adenoma.

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EP90

Vitamin D intake is major determinant of the concentration of 25-hydroxyvitamin D in the serum of healthy postmenopausal women.

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Objectives
The serum levels of 25-hydroxyvitamin D ([25 (OH) D]) is considered to be one of the most reliable biomarkers of vitamin D (VD) nutritional status. VD deficiency/insufficiency is a risk factor for osteoporotic fractures and falls. Even though established clinical significance of maintaining an adequate level of 25 (OH) D, the level of 25 (OH) D is easily fluctuated by diverse factors such as sunlight exposure, VD intake, renal function and body fat content. In addition, Fibroblast growth factor 23 (FGF23) has been shown to suppress and induce the conversion of 25 (OH) D to 1,25(OH)2D and to 24, 25 (OH)2D, respectively. These studies suggest that many other factors can influence the level of 25 (OH) D s. In the present study, we aimed to figure out factors that influence the level of 25 (OH) D in healthy postmenopausal women.
Methods
Two-hundred healthy postmenopausal women who had undergone osteoporosis screening were analyzed in this study. Serum levels of 25(OH)D, intact PTH, CTX, and FGF23 were measured. Bone mineral density (BMD) was measured using the DXA method at the lumbar vertebrae and femoral neck (FN). Nutrient intake was calculated using a food frequency questionnaire. Motor function tests included maximum step length (MSL), and grip strength.
Results
Mean values of age was 63.4 years with the following measurements: 25(OH)D 16.2±4.3 ng/ml, serum creatinine (Cr) 0.6±0.1 mg/dl, Ca intake 656±192 mg/day, VD intake 9.9±3.9 (range: 1.3–24.6) μg/day, MSL 102±13 cm, grip strength 21.8±4.5 kg, and the mean level of outdoor activity time 1.9±1.6 h (range: 0–7.0 h). The level of 25 (OH) D was significantly associated with the age and VD intake (P<0.001); unexpectedly the length of outdoor activity appeared to be insignificant association. Multiple regression analysis demonstrated that VD intake was associated with 25 (OH) D after adjusting for age, body mass index, body fat percentage, the levels of Ca, P, PTH, Cr, CTX, FGF23, BMD(FN), length of outdoor activity, other nutrients intake, MSL and grip strength (r=0.359, P=0.003).
Conclusion
VD intake significantly influenced the concentration of 25 (OH) D after adjusting for various factors including the body fat percentage and renal function. Our findings suggest that nutritional interventions focused on VD intake are important to ensure VD sufficiency.

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EP91

Vertebral fractures as first clinical manifestation of systemic mastocytosis in a young man

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Introduction
Systemic mastocytosis is a form of mastocytosis in which mast cells accumulate in tissues and organs such as liver, spleen, bone and small intestines. Symptoms and signs differ based on which parts of the body are affected and

vary from asymptomatic forms to highly aggresive forms with low survival rate. About 16% of patients with systemic mastocytosis have symptomatic fractures, but the presentation of systemic mastocytosis with vertebral fractures as first clinical sign in young men is rare.
Case report
A 37-year old man presented to endocrinology department after being diagnosed with two vertebral fractures (T6, T8) as a consequence of lifting an object weighing 10 kg. He was treated conservatively by the orthopedic surgeon. After endocrinological evaluation, osteoporosis was confimed by measurement of bone mineral density, with a T-score of −3.7 s.d. and a *Z*-score of −3.7 s.d. at lumbar spine. All hormonal tests for secondary osteoporosis were normal, but the level of serum tryptase was elevated. The patient was referred to the hematology department, where bone marrow biopsy and KIT D816V mutation test confirmed the diagnosis of systemic mastocytosis.
Conclusion
Non-traumatic vertebral fractures in apparently healthy young adults should raise the suspicion of an underlying pathology. Early identification and treatment of systemic mastocytosis could delay the progression of disease and prevent sequelae.

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EP92

Bone mineral density in patients with human immunodeficiency virus infection. Assessment of vitamin D status, treatment and other associated risk factors

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Introduction
In patients with human immunodeficiency virus (HIV) infection, the prevalence of osteoporosis is higher in comparison with the general population. Anti-retroviral therapy (ART) use seems to be a possible risk factor there is also high prevalence of vitamin D deficiency among people living with HIV.
Objectives
To describe bone mineral density (BMD) status in HIV-infected patients as well as its associated risk factors such as vit D levels.
Materials and methods
Retrospective observational study with a sample of 107 HIV-infected patients who underwent BMD evaluation.
Results
Baseline population results are summarized on the following table:

Características Basales	*n* (%), media (DS)
Males	79 (73.83%)
Age	55±7.3 años (a)
Weight	70.74±14.03 kg
Body mass index (BMI)	25.23±4.6 kg/m^2
Smokers	47 (43.9%)
Time since HIV-infected diagnosis	17.3±7.3 a
Antiretroviral therapy:	
• Tenofovir disproxil (TED)	91 (85%)
○ Treatment years	9.9±5.04 a
• Tenofovir alafenamide (TAF)	15 (14.01%)
○ Treatment years	1.83±2.12 a
• Protease inhibitors (PI)	31 (28.97%)
○ Treatment years	7.41±5.3 a
Parathyroid hormone (PTH)	47.5±26.5 ng/dl
Serum 25-OH-vitamin D (25-OH-VitD)	27±12.6 ng/ml
• Insufficiency (20–30 ng/ml)	43(40.1%)
• Deficiency (<20 ng/ml).	29 (27%)
Femoral neck	
• *T*-score	−1.3 ± 0.9
• *Z*-score	−0.5±0.9
Hip:	
• *T*-score	−0.8±0.8
• *Z*-score	−0.3±0.9
Lumbar spine:	
• *T*-score	−1.4±1.2
• *Z*-score	−0.8±1.25
Osteopenia:	
○ Femoral neck:	74 (69.1%)
○ Lumbar spine:	45 (42%)
Osteoporosis:	
○ Femoral neck:	10 (9.3%)
○ Lumbar spine:	20(18.6%)
Osteoporosis treatment	6 (5%) solo bifosfonatos
Vit D treatment	68 (63%)
Calcium supplements	2 (1.8%)
Evaluation by osteoporosis unit	21 (19.62%)

A statistically significant association was found between combined treatment with TED+PI and lower femoral neck and hip BMD and femoral neck osteopenia. Longer duration of treatment was associated with femoral neck osteopenia and lower BMD at the femoral neck and lumbar spine. 25-OH-VitD deficiency was associated with overall lower BMD at the femoral neck and hip.
Conclusions
HIV-infected patients show a high prevalence of osteopenia and osteoporosis. Combined use of TED+PI, longer duration of ART treatment and long-standing HIV infection could be possible risk factors for this finding. There is a high prevalence of vitamin D insufficiency/deficiency despite a high prescription of supplementation.

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EP93

Fibrodysplasia ossificans progressiva: Cobbling together a treatment plan for a patient with osteomyelitis

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Introduction
We describe a patient with Fibrodysplasia ossificans progressiva (FOP) who developed an osteomyelitic neuropathic toe ulcer. This was treated effectively with conservative measures, but highlighted the need for multiprofessional working in managing patients with FOP.
Case
The patient's toe ulcer occurred in 2017 and was initially managed by community podiatry and orthopaedics. The patient received multiple courses of antibiotics for recurrent infection. In 2018 they were reviewed in an endocrine clinic for a different reason whereby the osteomyeltic ulcer was highlighted. At the time the orthopaedic team were contemplating surgical debridement of the toe under spinal anaesthesia. A request for the patient to be seen in the diabetes foot clinic as an exceptional non-diabetic case was made. Initial assessment determined that there was a fixed flexion ankle deformity secondary to the FOP which was causing pressure on the first and second toes. Occupational Therapy were unable to provide a temporary device to offload such deformity and the orthotic department were asked to design a bespoke moulded insole with orthotic shoe. The infection was treated with a prolonged course of oral antibiotics and regular reviews. The combination of effective antibiotics and orthotic offloading has resolved the ulcer and osteomyelitis.
Discussion
FOP is an rare autosomal dominant condition in which there is a tendency for muscle and connective tissue to be replaced with bone, particularly in response to trauma. Specific dilemmas arose during treatment of this patient in terms of surgical and anaesthetic considerations, radiological imaging,

monitoring for flares in FOP and subsequent advise to other professionals involved in the patients care, which recently included a dentist. The learning points from the management of this case could be applied to the treatment of other patients with similar challenges.

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EP94

Effect of Denosumab on bone mineral density of hematopoietic stem cell transplantation recipients

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Purpose
Denosumab is a monoclonal antibody that prevents osteoclast development. The effect of denosumab in solid organ transplant recipients has been elucidated, but the effect of denosumab in hematopoietic stem cell transplantation recipients has not been studied yet. Thus, the aim of this study was to determine the effectiveness and safety of denosumab in hematopoietic stem cell transplantation recipients.
Methods
We retrospectively evaluated 27 patients with osteoporosis (8 males and 19 females, mean age 53.6±12.8 years) following allogeneic hematopoietic stem cell transplantation. Patients were treated with denosumab every 6 months for 12 months. The period of time since previous transplantations ranged from 2 years to 14 years (mean: 5.1±2.7 years). Osteoporosis was diagnosed using dual energy X-ray absorptiometry. Bone mineral density was evaluated for denosumab-treated patients in a 12-month interval after the first administration of denosumab.
Results
Significant increases in bone mineral density were observed in all measured skeletal sites: 4.39±6.63% for the lumbar spine ($P=0.014$), 3.11±7.69% for the femoral neck ($P=0.048$), and 1.97±6.01% for the total hip ($P=0.138$). The bone turnover marker serum cross-linked C-terminal telopeptide of type 1 collagen decreased at 12 months, without significance (−6.67±31.57%, $P=0.58$). No serious symptomatic hypocalcemia was observed. However, asymptomatic hypocalcemia was noted in 2 (7.4%) patients. Serious adverse drug reactions requiring drug discontinuation were not observed.
Conclusion
Denosumab was well tolerated. It improved bone mineral density of hematopoietic stem cell transplantation recipients.
Keywords: Denosumab; Hematopoietic stem cell transplantation; Bone density; Osteoporosis

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EP95

Synchronous parathyroid carcinoma and papillary thyroid carcinoma: A case report

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Introduction
In 1974, the first case of concomitant thyroid and parathyroid disease was reported. Non-medullary thyroid carcinoma has been reported in 6% of patients with Primary hyperparathyroidism. However, the simultaneous occurrence of parathyroid carcinoma along with non-medullary thyroid carcinoma is extremely rare.
Case report
We report a case of 60-year-old woman with a history of Diabetes Mellitus type 2 and hypertension. She had no family history of thyroid cancer or multiple endocrine neoplasia type 1 or 2. She presented with symptoms of severe hypercalcemia with calcium level at 13.83 mg/l (8.8–10.4 mg/l) and had increased serum parathyroid hormone level (569 pg/ml). Physical examination revealed an approximately 3 cm left nodular thyroid without recurrent nerve palsy or cervical lymphadenopathy. A bone density test performed showed no evidence osteoporosis. On ultrasound of the neck, her thyroid was multinodular with a 4–10 mm highly hypoechoic nodules associated with a large nodule at the upper pole of the left thyroid which measured 3 cm. Technetium-99 m methoxyisobutylisonitrile (MIBI) cervical and mediastinal substraction scintigraphy scans revealed increased uptake of left polar superior area of thyroid. Blood and urine tests and calcitonin levels were normal, making multiple endocrine neoplasia type 2 very unlikely. The patient received a total thyroidectomy, left parathyroidectomy, and central and lateral cervical lymph node dissection were performed in consideration of extemporaneous histological examination suggestive of a papillary micro-carcinoma of the left lobe and the suspicious aspect of the 4 cm parathyroid formation which was hard and adherent to the thyroid and difficult to dissect from the vascular axis. The definitive anatomopathological examination of the operative specimen showed a bifocal papillary micro carcinoma with vesicular component. The left parathyroid gland was the site of significant multinodular hyperplasia with central nodule involvement with vascular emboli and capsular invasion. Considering the severity of the hypercalcemia and macroscopic appearance as well as the histological aspect, the diagnosis of parathyroid carcinoma was retained. Postoperatively, the patient had normocalcemia in conjunction with PTH levels measured 30 pg/ml. Investigations showed no distant metastasis.
Conclusion
In conclusion incidence of primary hyperparathyroidism due to parathyroid carcinoma along with non-medullary thyroid carcinoma is extremely rare. In patients with severe hypercalcemia, parathyroid carcinoma should be considered a possible underlying cause, and if the operative finding supports the suspicion of parathyroid carcinoma, an en bloc resection of the parathyroid tumor and the adjacent thyroid lobe should be performed.

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EP96

Epilepsy – Fahr syndrome – Primary hypoparathyroidism: A diagnostic journey

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Background
Fahr syndrome is a rare entity characterized by symmetrical bilateral brain calcifications, involving basal ganglia (mainly), thalami, dentate nuclei and the cerebral and cerebellar white matter. Progressive neurologic dysfunction and other neuropsychiatric disorders are characteristic. Endocrine disorders which may present with Fahr syndrome include parathyroid dysfunction (hypoparathyroidism especially, but also pseudohypoparathyroidism, pseudopseudohypoparathyroidism and hyperparathyroidism) and vitamin D deficiency.
Case report
We present the case of a 22-year-old male patient, referred for evaluation from the Neurology department. He came from non-cosanguineous parents, had a healthy 15-year-old sister and the mother reported normal pregnancy, delivery and development; at age 7, he was diagnosed with epilepsy with generalized tonic–clonic seizures, following an episode of infectious meningo-encephalitis. He received various antiepileptic drugs during the following years (carbamazepine, valproic acid, levetiracetam) with weak seizure control. From the patient's medical history, we highlight recurrent episodes of hypocalcemia (e.g. 3.26 mg/dl (8.4–10.2) at age 9), right eye surgery for posterior subcapsular cataract at age 21 and mild mental impairment. Despite being advised to seek endocrinological assessment, the mother failed to do so. During neurologic evaluation, brain scan revealed extensive symmetrical calcifications, concerning basal ganglia, thalami, dentate nuclei, cerebral and cerebellar white matter, highly suggestive for Fahr syndrome. Physical examination revealed resting and intentional tremor, tetra-ataxia and cogwheel rigidity. EEG revealed non-specific changes. On admission in our clinic, calcium levels were 4.36 mg/dl (normoalbuminemia), phosphate 10 mg/dl (2.5–4.5), magnesium 1.41 mg/dl (1.6–2.6), 24 h calciuria 69 mg (5–300) and parathormone 2.66 pg/ml (15–65). Vitamin D was normal and no other hormone deficiencies, nor thyroid autoimmunity were associated. Ophtalmologic examination revealed posterior subcapsular left eye cataract, with surgical treatment indication. A diagnosis of primary hypoparathyroidism (PH) was established and treatment with alphacalcidol, calcium and magnesium supplements, along with valproic acid and levetiracetam was recommended. 6 months later, the patient demonstrated normal calcium and magnesium levels, a phosphate of 5.7 mg/dl, marked amelioration of tremor and reported seizure cessation. He received indications for gradual valproate withdrawal, but given the extensive nature of cerebral calcifications and the persistence of non-specific EEG changes, chronic levetiracetam treatment was recommended.

Discussions and conclusion
PH may associate Fahr syndrome, along with chronic hypocalcemia, both of which may trigger epileptic seizures. Diagnosing PH in an already complicated form, in context of longstanding intractable epilepsy is rare and undesirable, but timely treatment may greatly improve epileptic manifestations, in spite of extensive cerebral calcifications and is essential in order to avoid further aggravation.

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EP97

Hyperparathyroidism in the internal medicine department

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Introduction
Hyperparathyroidism is defined by excessive secretion of parathyroid hormone (PTH) that is responsible for calcium regulation. Hyperparathyroidism can be primary in which the gland is affected and it produces PTH excessively or secondary or tertiary that cause hypersecretion of PTH as a regulatory response. The aim of our study was to describe patients with hyperparathyroidise diagnosed in internal medicine departement.
Methods
It was a retrospective descriptive study about patients hospitalized in the internal medicine ward between 2009 and 2019 and diagnosed with hyperparathyroidism.
Results
our study interested 12 patients with 3 men and 9 women. Mean age was 58 [35–80]. Three of them were hospitalized for malignant hypercalcemia. The other causes of hospitalisations were: flush Syndrom ($n=1$), severe malabsorption ($n=1$), profound anemia ($n=1$), deterioration of the general status ($n=3$) and a diagnosed systemic disease ($n=3$). Medical history included kidney failure($n=7$) ,hypertension($n=3$), diabetes($n=2$),urinary lithiasis($n=2$), cardiac rhythm disorders ($n=3$) and one of the patients had several episodes of pancreatitis.
– primary hyperparathyroidism was diagnosed in five patients.
– secondary hyperparathyroidism caused by kidney failure was diagnosed in 6 patients and the cause – was severe malabsorption due to coeliac disease in one case.
– general manifestations were the most to be found :weigh loss and asthenia ($n=10$) Digestive signs such as epigastric pain and nausea ($n=8$) with two cases of chronic gastritis.
Cervical echography showed the presence of thyroid nodule in five cases, with hypothyroidism for one of them. For one patient we found microprolactinoma and she is suspected to be a case of NEM1. Patients with primary hyperparathyroidism went through surgery with positive outcomes, when in secondary hyperparathyroidism calcium substitution was initiated.
Conclusion
Hyperparathyroidism is a common endocrine disease that can be asymptomatic or can be present with non-specific signs, but it can have severe manifestations and complications. It is frequent in adults and the elderly. This disease should be recognized at early stages to initiate optimal therapeutic strategy and have better outcomes such as reduced cardiovascular disease and improved survival.

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EP98

Primary hyperparathyroidism and Gougerot disease: A case report

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Introduction
Gougerot disease is an autoimmune disorder characterized by the lymphoid infiltration of salivary and lachrymal glands leading to the two most common symptoms dry eyes and a dry mouth. Primary hyperparathyroidism (PHPT), one of the most common endocrine disorders, is usually diagnosed by the association of hypercalcemia and parathyroid hormone (PTH) levels that are either elevated or inappropriately normal. The association of PHPT with Gougerot disease is rare, only few cases were reported in the literature. Herein we report the case of a female patient diagnosed with PHPT and Gougerot Disease.
Observation
A 60-year-old woman with no past medical history was admitted to our department to explore hypercalcemia and renal failure. The aboratory investigations revealed severe hypercalcemia (3.6 mmol/l), hypophosphatemia (0.54 mmol/l), and elevated PTH level (569 pg/ml). Cervical ultrasonography showed no parathyroid lesion but sestamibi sintigraphy reveled a voluminous left superior parathyroid adenoma. A surgical treatment of the parathyroid adenoma was then performed. However, the patient complained of dry eyes and a dry mouth of few month of duration. The diagnosis of Gougerot disease was confirmed by the association of xerostomy; anti-SSa- and anti-SSb-positive, and Chisholm stage IV lymphocytic sialadenitis. The etiological investigation confirmed a primary Gougerot disease.
Conclusion
The association between PHPT and Gougerot disease is reported in literature but up to date no etiopathogenetic links between the two affections were found.

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EP99

Idiopathic Hypoparathyroidism – An uncommon cause of a chest pain

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Introduction
Hypocalcemia has been linked to a decreased myocardial performance and even congestive heart failure, while acute chest-pain as leading symptom of hypocalcemia is an unusual presentation.
Case report
A 29-year-old Caucasian man presented to the emergency department with relapsing chest-pain since several days, lasting seconds sometimes lasting several minutes, radiating to the left shoulder and combined with mild tingling in the neck. A detailed history revealed occasional muscle cramps on exercise or due to long sitting in one position. The patient also felt tired and had sleep disturbances. His medical history was unremarkable and he never underwent an operation. In the family history, nephrolithiasis in the grandfather and the great-grand father was striking. The initial physical examination revealed no pathologies, the blood pressure and heart rate were normal. The ECG showed a prolonged QTc of 465 ms but was otherwise unremarkable. The laboratory findings showed normal results (complete blood count, renal and liver function tests, markers of inflammation, high sensitive Troponin T and D-dimers) except of a severe hypocalcemia (total calcium: 1.42 nmol/l albumin-adjusted: of 1.5 nmol/l, ionized 0.76 nmol/l) and hyperphosphatemia of 2.09 nmol/l. Further tests revealed a magnesemia of 0.7 nmol/l, a Vitamin-D of 27 nmol/l and iPTH of 14.9 ng/l (reference range: 15.0–65.0 ng/l). The TSH was 1.68 mIU/l; the urinary excretion of calcium (0.8 mmol/l) was low. Based on these results, we established a diagnosis of idiopathic hypoparathyroidism and started a therapy with calcitriol (initial dose 0.25 µg twice daily, later increased to 0.25 µg three times a day) and calcium and magnesium supplementation (2 g/d and 10 mmol/d, respectively). Already the next day on the therapy, the symptoms vanished and the patient could be discharged. In further follow-up, normal calcium and phosphate values could be reached. Screening for possible associated organ-specific autoimmune diseases was negative and there were no signs of candidiasis. There were no signs of hemochromatosis or infiltrative/granulomatous disease.
Discussion
Here we present a rare case of idiopathic hypoparathyroidism which probably proceeded over years until presentation with severe relapsing chest pain. Chronic severe hypocalcemia can present like an acute coronary syndrome. The cause remains unclear; a possible autoimmune background cannot be excluded.

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EP100

Nonmedullary hypercalcitoninemia in a hypocalcemic patient: Shoud we look at serum calcitonin level in the differantial diagnosis of hypocalcemia?

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Background
Although high levels of calcitonin suggest neoplastic proliferations such as medullary thyroid carcinoma, C cell hyperplasia and some neuroendocrine tumors, systemic diseases and drugs may also elevate calcitonin. Although calcitonin is not as effective as PTH, it has got a role in calcium hemoastasis. Supraphysiological calcitonin level can lead to hypocalcemia.
Case presentation
A 57-year-old male patient was diagnosed with epilepsy with complaints of contraction in the body at the age of 16. Phenytoin therapy was started. He had no epileptic seizures for 13 years. Basal ganglia calcification was detected in brain CT which had been taken when he had muscle contractions while he had been hospitalized for measles in 1992. Calcium: 6.9 mg/dl phosphorus: 5.3 mg/dl albumin: 4.7 g/dl, parathormone: 499 pmol/l (219–659) calcitonin: 145 (0–50) was measured and hypoparathyroidism was diagnosed. Calcitriol and calcium carbonate treatment had been started. In another medical center it was thought that he had pseudohipoparathyroidism, because calcium was normal, vitamin D and parathormone were high while he was not taking calcium replacement treatment. He came to outpatient clinic in 2018 while he was taking 2000 mg oral calcium carbonate treatment. Calcium: 8.9 mg/dl (8.7–10.4) phosphorus:3.5 mg/dl albumin:4.5 g/dl, parathormone: 41 ng/l (18–80), 25-OH vitamin D: 41 ng/ml (25–80), 1,25OH vitamin D: 24.1 pg/ml (18–64) kalsitonin:117 ng/l (<8.4) was measured. Pseudohipoparathyroidism wasn't considered with clinical findings. The control calcitonin value was 144, and the highest calcitonin value was 323. Thyroid USG and CEA levels were normal. He had no medullary thyroid carcinoma history in the family. CDKN1B, RET, menin gene analysis were normal. 24-h urinary calcium was 55 mg/day. The heterophile antibody examined by the PEG precipitation method and heterophile antibody-coated tube was negative. No pathological lesions were detected in GA-68 DOTA peptide imaging performed for possible neuroendocrine tumor.
Conclusion
In cases of hypercalcitoninemia, C cell neoplasms should be investigated primarily. In this case, medullary thyroid carcinoma was not considered with the current findings. Due to the coexistence of hypocalcemia and endogenous hypercalcitonemia, the possibility of autosomal dominant hypocalcemia was considered in which calcium sensing receptor activation is playing a role. However, hypocalcuria was interpreted against this possibility. In case of low/normal parathormone in the etiology of hypocalcemia, it is also suggested to measure the calcitonin level.

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EP101

Management of primary hyperparathyroidism in pregnancy

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Introduction
In pregnancy, the incidence of Primary Hyperparathyroidism is 1%; and there are 80% adenoma, 15% parathyroid hyperplasia, 3% multiple adenoma, and 1% parathyroid carcinoma in its etiology. In pregnancy, serum calcium (Ca) levels may not rise as much as expected. This is associated with hypoalbuminemia, GFR increase, placental Ca transfer, and inhibition of PTH–related bone resorption by estrogen. In pregnancy, hyperparathyroidism is asymptomatic at a rate of 25–80%. In pregnancies that are complicated with primary hyperparathyroidism, 67% maternal and 80% fetal/neonatal complications were reported in previous studies. In this case report, a pregnant patient who was followed-up due to primary hyperparathyroidism has been presented.
Case
A 34-year-old female patient, who had a history of operation in 2013 and 2018 because of nephrolithiasis, was referred to our clinic in January 2019 because of hypercalcemia. The patient had Ca:11.66 mg/dl (8.7–10.4 mg/dl), Pth:163 ng/l (18.4–80.1 ng/l), P:2.74 mg/dl (2.4–5.1 mg/dl), alb: 48 g/l (32–48 g/l). The Ca elimination in 24-hour urine was 131 mg/day. In the USG, Hypoechoic nodular formation was detected outside the left lobe inferior thyroid area (LAP? PARATHYROID ADENOMA?); and there was a finding that was consistent with adenoma in the same localization in the MIBI. The Z score of the patient was consistent with age and gender. In renal USI, 5–mm diameter stone was detected in the right kidney. Hormonal evaluation was made in terms of multiple endocrine neoplasia. Sampling was made for genetics. When the genetic results were expected, it was determined that the patient was pregnant in May 2019. The patient who had Ca: 11 mg/dl (8.7–10.4 mg/dl), alb:41 g/l (32–48 g/l), P: 2.1 mg/dl (2.4–5.1 mg/dl), was admitted to the Endocrine Service on 20/06/2019. The patient was given oral and iv hydration after which it was detected that Ca:9.910.5 mg/dl (D.Ca: 9.9–10.5 mg/dl). Parathyroid adenectomy+left thyroid lobectomy surgery was performed on 16/7/19 while the patient was still pregnant at 23 weeks. Her pathology resulted as Parathyroid Adenoma. After the operation, Ca: 8.8 mg/dl (8.7–10.4 mg/dl), dCa: 9.2 mg/dl, mg: 1.4 mg/dl (1.3–2.7 mg/dl), PTH 26 ng/l (18.4–80.1 ng/l), were detected. When the patient was at 39th week, she gave birth to a 2.500–kg girl with a caesarean section on 20/11/2019.
Conclusion
The decision to medical or surgical treatment of Primary Hyperparathyroidism in pregnant women is based on the evaluation of the risks by the endocrinologist and the obstetrician. The definitive treatment is surgery. Serum Ca: 2.75 mmol/l (11 mg/dl) and/or hypercalcemia is recommended for the treatment of maternal or fetal complications. Surgery is recommended in the 2nd trimester.

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EP102

A case of hypoparathyroidism, sensorineural deafness and renal disease (HDR) syndrome in a boy carrying a novel mutation of GATA3 gene

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HDR syndrome is a rare condition with an autosomic dominant inheritance, firstly described in 1977. It is due to a mutation of *GATA3* gene, a transcription factor expressed in parathyroid, inner ear, kidney, central nervous system and T lymphocytes. The most common manifestation is neurosensorial deaf, secondary to progressive degeneration of coclear cells. Hypoparathyroidism is present in 90% of patients that can be asymptomatic or, sometimes presents with neuromuscular, cardiac or cognitive symptoms. Kidney manifestions namely renal hypoplasia, renal cysts, tubular acidosis are less common. Other rarer manifestations are neurological and genital malformations, psoriasis and intestinal, cardiac and craniofacial defects. We report the case of a 17 yrs-old boy, who was referred to our Department in May 2018 for hypocalcemia incidentally detected at routine blood tests. The clinical history was unremarkable except for sporadic paresthesia. He successfully played agonistic sport. No cognitive symptoms were present, At physical examination he appeared in good general condition without cleft palate or signs of chronic candidiasis. Trousseau and Chvosteck signs were positive. Biochemical evaluation showed a severe hypocalcemia [albumin–corrected serum calcium 5.3 mg/dl (8.6–10.2) and ionized calcium 0.62 mmol/l (1.13–1.32)], undetectable PTH levels [< 4 pg/ml (8–40)] and normal 25–OH vitamin D level [26.6 µg/l]. He had since age 12 psoriasis treated with topical therapy. Computed tomography displayed multiple cerebral calcifications. Abdomen ultrasound and magnetic resonance imaging showed multiple renal cysts, the largest of which was 6.5 cm. Audiometric examination exhibited a sensorineural hearing loss. No cardiac alterations were detected at ECG and echocardiography. Taking into account the clinical and biochemical data an *HDR* syndrome was suspected. due to a mutation of *GATA3* gene was suspected. Family history was remarkable for hypocalcemic disorders. Genetic analysis of *GATA 3* gene in the proband showed a heterozygous mutation in exon 3 (c.404dupC) leading to a frameshift and a truncated protein (p.Ala136GlyfsTer168).The mutation was not identified in the proband parent's indicating that the mutation was "de novo". In conclusion, we describe a case of sporadic hypoparathyroidism due to HDR syndrome. This condition, although rare, must be suspected on the basis of clinical evidences and confirmed with genetic analysis. Our patient in on treatment with calcium carbonate and calcitriol, with a good control of serum calcium level and 24 h–urinary calcium excretion.

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EP103

Use of alfacalcidol and teriparatide for postsurgical hypoparathyroidism in a patient with gastrostomy and toxicity after systemic antineoplastic therapy: A case report

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Introduction
Post-surgical hypoparathyroidism (PSHP) is a frequent complication following ENT surgery. Some patients with head/neck cancers require enteral nutrition (EN) due to dysphagia, mucositis after radiotherapy or chemotherapy, or post-surgical anatomical complications. Formulas of calcitriol are not suitable to be administered via enteral feeding tubes, and side effects of systemic antineoplastic treatment (nausea, vomiting) make calcium and phosphate serum levels difficult to maintain in the presence of PSHP.
Case Report
We present the case of a 44–year–old male with a squamous cell carcinoma of the vocal cord stage IIIB (T3N1M0) treated with radiotherapy and chemotherapy until February 2018. After eight months he presented with local relapse. Total laryngectomy, partial esophagostomy and total thyroidectomy were performed. Due to a laryngo-pharyngeal fistula with multiple failed surgical attempts of closure associating long-term dysphagia, a percutaneous radiologic gastrostomy (PRG) was placed. The Endocrinology department was consulted for management of hypothyroidism and PSHP requiring intravenous calcium supplementation, with the following laboratory results: calcium (corrected) 6 mg/dl (8.5–10.5), phosphate 4.1 mg/dl(2.5–4.5), magnesium 1.8 mg/dl (1.72.6), 25OH-vitamin D 24.8 ng/ml(30–100), iPTH 7.2 pg/ml (15–65), TSH 52.54 uIU/ml (0.38–5.33), FT4 5.4 pg/ml(5.8–16.4). Treatment via PRG was initiated with alfacalcidol 2 μg/ml (Etalpha): 2 μg/24 h; calcium acetate 500 mg–127 mg elemental calcium (Royen):1500 mg/8 h (1143 mg elemental calcium/24 h); magnesium lactate 97.24 mg/24 h; levothyroxine 150 μg/24 h. After 20 days of treatment: calcium 8.2 mg/dl, phosphate 4.1 mg/dl, magnesium 1.7 mg/dl, 25OH-vitamin D 32.7 ng/ml, calciuria 0.11 mg/ mgCr24h, TSH 4.15 uIU/ml, FT4 9.62 pg/ml. After twelve months he received chemotherapy due to local relapse, subsequently presenting with emesis and positive Trousseau sign, calcium 6.9 mg/dl, phosphate 6.2 mg/dl, magnesium 1.5 mg/dl, iPTH 5.6 pg/ml. Symptomatic hypocalcemia was persistent despite intravenous calcium supplementation. Off–label treatment was initiated with teriparatide (Forsteo):20 μg/24 h subcutaneous, initially simultaneous with intravenous calcium. After 15 days: calcium 8.5 mg/dl, phosphate 3.3 mg/dl, magnesium 1.5 mg/dl, which allowed for ceasing intravenous calcium and weaning enteral supply of calcium and vitamin D.
Discussion
Management of PSHP in patients with dysphagia is complex due to the contraindication to administer calcitriol via gastrostomy. Alfacalcidol is an active form of vitamin D with 1-hydroxlation requiring hepatic 25-hydroxilation (PTH-independent), and can be administered via gastrostomy. Despite minimal experience with its use, it was effective in our patient for the management of hypocalcemia until the later appearance of chemotherapy-related emesis. Teriparatide is recombinant human PTH (1–34) currently approved for treatment of osteoporosis in postmenopausal women. However, teriparatide may be used off-label in certain patients with hypoparathyroidism who cannot tolerate oral nor enteral calcium and vitamin D in order to achieve and maintain calcium-phosphate homeostasis.

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EP104

Subtotal parathyroidectomy for the treatment of tertiary hyperparathyroidism

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Tertiary hyperparathyroidism reflects parathyroid hyperplasia, with autonomous secretion of parathyroid hormone (PTH), in spite of high plasma calcium concentration. Parathyroidectomy is an efficient therapy for stabilization of calcium and PTH metabolism in patients with end-stage kidney disease.
We report a case of a 68-year old man with end-stage kidney disease under hemodialysis for nine years, due to long-standing uncontrolled hypertension. He presented with high total plasma calcium levels (11.0 mg/dl) and high serum PTH (2638 pg/ml), regardless of therapy with cinacalcet. Parathyroid scintigraphy revealed a hyperfunctioning lower right parathyroid. Cervical CT-scan was consistent with enlargement of both right and left inferior parathyroid glands. Patient underwent successful subtotal parathyroidectomy, with reduction in intra-operative PTH from 2996 pg/ml to 364 pg/ml. After surgery plasma calcium levels fell to 7.1 mg/dl, but remained stable afterwards under supplementation with calcium carbonate and calcitriol.
Refractory hyperparathyroidism in patients with end-stage kidney disease is associated with bone and joint pain and/or fractures, muscle weakness, extraskeletal calcification and calciphylaxis. Parathyroidectomy ameliorates symptoms and stabilizes calcium and phosphorus levels, as seen in this case.

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EP105

A case of hyperparathyroidism due to ntrathorcic lipoadenoma

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Lipoadenoma is an uncommon benign lesión of the parathyroid gland (<1%) and it has most commonly described as non-functional, but also is a very rare cause of primary hyperparathyroidism. Since 1958 scientific literatura had described 54 cases all over the world and only six of that paratyroid lipoadenomas was extended into torax. A case of intrathoracic parathyroid lipoadenoma with hyperparathyroidism is described. A 69–year–old man was refered to our hospital for hypercalcemia and primary hyperparathyroidism. By that time he was asymptomatic and was only treated with enalapril 10 mg per day. Laboratory tests revealed hypercalcemia (11.7 mg/dl), hypercalciuria (24 h urine calcium=574 mg/day), hypophosphatemia (2.0 mg/dl), elevated serum parathyroid hormone level (PTH=284.8 pg/dl), low 25 hydroxy vitamin D (25 OH D=9 pg/ml) and glomerular filtration rate (GFR)=79 ml/min. Parathyroid technetium–99n sestamibi scintigraphy failed to detect increased activity in the right lower pole of the thyroid, and that abnormal lession was extending into the superior mediastinum. SPECT–TC showed a nodule 45×24×62 mm hyperfunctioning behind the right thyroid lobe and extended into medistinum.
The patient accepted the surgery, so the tumor was excised. His serum calcium flollowing successfull inferior right parathyroidectomy was 9.6 mg/dl. After surgery, serum Calcium and PTH normalized to 8.5 mg/dl and 41.7 pg/dl respectively.
The pathological diagnosis was parathyroid lipoadenoma with abundant adipose and nests of chief cells.

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EP106

Parathyroid cancer: Clinical case

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Background
Parathyroid cancer is a rare pathology, approximately 2 cases per 10, 000, 000 people/year. The five-year survival rate for this disease ranges from 20–85%, and the ten-year survival rate is approximately 15–80%. Timely detection and compliance with algorithms for parathyroid gland cancer diagnostics allows surgical treatment and maximum positive prognosis for patient.
Clinical cаse
Patient 18 y.o., was presented with complaints to aching pains in the bones and joints, repeated fractures of the bones with a fall from the height of the body. It was found out from medical history that patient marked this complaints at 2016. Youthful osteochondrosis was diagnosed by orthopedist of the large and small tibia, symptomatic therapy was performed without improvement. A fracture of the ulnar bone of the left arm was occurred after fall from the height of his own growth. A swelling in the anterior region of 1, 2, 3 ribs on the right, when chest radiography was performed and myeloma was suspected. On the results of myelography this pathology was excluded. Intensive accumulation of the drug in the bones of the cranial vault was not-

ed on osteoscintigraphy, thus primary hyperparathyroidism was suspected.
Patient was hospitalized. Increased levels of PTH (2252 pg/ml), total calcium (3.06 mmol/l) and calcium ionized (1.66 nmol/l) were determined. At palpation, thyroid gland was enlarged, elastic volumetric formation is palpable on the right, so ultrasonography of thyroid and parathyroid glands was performed. At the result volumetric formation behind a capsule of the thyroid gland 35 × 32 mm in size was found. The tumor from the follicular epithelium was verified by fine needle aspiration biopsy, probably it was an adenoma. According to scintigraphy with 99 mTc, signs of large hyperfunction formation of parathyroid tissue / probably originating from the left lower parathyroid gland.
Thus, primary hyperparathyroidism was verified and surgical treatment was recommended.
The left lower parathyroid gland with a tumor was removed. According to histological study, parathyroid cancer was detected with foci of invasion into the tumor capsule.
Patient was discharged from the hospital with the final diagnosis of "Carcinoma of the left lower parathyroid gland" and recommendations: control of ionized calcium, phosphorus, PTH after 1 week.
Conclusion
This clinical case demonstrates that the correct interpreting of a clinical picture and keeping of algorithms of diagnostics allowed well-timed to tap parathyroid cancer of the young man and to carry out surgical treatment that allows hoping for the most positive forecast for this patient.

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EP107

Ectopic parathyroid hormone secretion by a squamous cell carcinoma of the floor of the mouth with poor response to cinacalcet

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Introduction
Ectopic PTH secretion is rare, to our knowledge, with only 27 cases reported in the literature and 3, (a tonsil, a lung and a penile) due to squamous cell carcinoma .In the few cases reported to date it appears to be more common in males and in those over the age of 60. The management of the hypercalcemia in this setting is complicated. We are aware of 2 other case reports in which cinacalcet was used in this context, but as in our case, unsuccessfully.
Case Report
A 75 year old man, with a previous history of a stage IVA(T4a N0M0) squamous cell carcinoma of the floor of the mouth that was in progression 2 months prior to being admitted, presenting a 1 week history of malaise due to severe hypercalcemia(previous levels were normal) The patient did not have evidence of bony metastatic disease on imaging studies. Further laboratory evaluation revealed PTHrP of < 1.1 pmol/l (0–1.5), increase PTH level of 404 pg/ml (10–65), and 25-OH vitamin D level of 16 ng/ml (30–80), 1.25 Dihidroxi vitamin D 37 pg/ml (25–66), consistent with PTH dependent hypercalcemia Ultrasonography, Technetium 99 scanning, and CT examination of the neck and chest failed to identify adenoma, hyperplasia or an ectopic parathyroid gland. We therefore considered the possibility of an ectopic source of PTH. Immunohistochemical staining for PTH in cytology was attempted in our patient, however this was negative .This result may have been due to the quality of the sample .A biopsy of the primary mass was not performed as the procedure was not in the best interest of the patient due to the patient's rapidly worsening condition. Inspite of therapy with fluids, cinacalcet, zolendronic acid, the patient remained hypercalcemic, observing an increase in PTH as an "escape phenomenon" . The patient died a month after his diagnosis.
Conclusion
It is important to look for alternative etiologies in cases of hypercalcemia in the setting of malignancy including both PTHrp related and paraneoplastic ectopic secretion of PTH.
The management of the hypercalcemia in this setting is complicated and often times associated to poor prognosis. A better prognosis and management of hypercalcemia in this context, is related to the treatment of the malignancy, with surgery or chemotherapy. More studies are needed to determine whether there is a role for calcimimetics in this context.

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EP108

Sequential treatment of osteoporosis: Our clinical experience

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Backgroud
When considering treatment of patients with severe osteoporosis (after previously failed antiresorptive treatment) or patients with glucocorticoid–induced osteoporosis, it is suitable to choose treatment by teriparatide (TPTD, rhPTH 1–34). In contrast to long–term treatment by bisphosphonates (BP) or denosumab (DMAB), the treatment with TPTD increases the volume of trabecular bone and the thickness of cortical bone. The recommended length of treatment is 24 months necessarily followed by an antiresorptive treatment in order to prevent loss of newly gained bone mass.
Methods
The study sample included women with severe postmenopausal osteoporosis (PMO, $n=14$) and patients with glucocorticoid-induced osteoporosis (GIO, $n=37$) who finished two-year TPTD treatment. At baseline visit (after discontinuation of TPTD treatment) were measured BMD of lumbar spine, hip and distal forearm and biochemical markers of bone turnover (serum intact amino-terminal propeptide of type I procollagen, type 1 collagen cross-linked C-telopeptide). A follow-up visit was performed anually during treatment by DMAB (Prolia 60 mg s.c. once per 6 months) or treatment by risedronate (Risendros tablets 35 mg/weekly). All patients received vitamin D substitution (cholecalciferol 1000–4000 IU/daily) and calcium (500–1000 mg/daily).
Results
Patients with PMO treated with TPTD for 2 years followed by 4 years of DMAB treatment ($n=14$) increased lumbar spine BMD +19.5% and total femur BMD+6.2% during the 6–year study period. Patients with GIO treated by DMAB ($n=10$) increased lumbar spine BMD+11.7% and total femur BMD+4.5% in the same period. The group of patients with GIO treated by risedronate ($n=27$) gained 9.7% in the lumbar spine BMD and 2.5% in total femur BMD during this period. The TPTD treatment invoked comparable increase in lumbar spine BMD and total femur BMD in both PMO and GIO patients in the first two years of the study. The following 4 years of DMAB treatment induced notably higher increase in lumbar spine BMD and total femur BMD in PMO patients compared to GIO patients. Treatment with risedronate resulted in a comparable increase in lumbar spine BMD in GIO patients, but a decrease in total femur BMD after the first year of treatment was detected.
Conclusion
Results from non-selective group of patients from ordinary clinical practice demonstrated that the response to treatment is significantly influenced by other risk factors (e.g. treatment of glucocorticoids, immobility, etc.) For patients with a very high risk of fragility fracture, the sequential treatment with TPTD should be the primary osteoporosis treatment choice.

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EP109

Hip fracture and the brown tumors as clinical manifestation of primary hyperparathyroidism in late reproductive age woman: Case report.

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Purpose
Primary hyperparathyroidism (PHPT) is the third common endocrine disorder which often manifest with skeletal or renal disfunction. In developed countries asymptomatic form is the most common and such severe manifestations as osteofibrosis cystica are very rare.
Clinical case
We present the case of 49-years-75 × 66 old caucasian woman, with history of urolithiasis, nephrolithotripsy in 2014. In November 2016 she was diagnosed with left femur fracture. The X-ray showed multiple lesions of bone resorption in the right radius, left and right femurs, left humerus and pelvic bones. Locked intramedullary osteosynthesis was performed. In spring 2017 limitation of mobility in right forearm and severe bone pain appeared. The PTH level was 1859 pg/ml (15–65), serum ionized calcium level was 2.20 (1.11–1.32). Bone scan showed lesions of increased uptake in skull, pelvic, right forearm bones and in femurs. CT–scan showed multiple massive

tumor-like deformities of the left ilium and nadacetular region measuring 75 × 66 × 42 mm (+ 22 HU), of the right pubic bone and the right acetabulum measuring 40 × 37 × 31 mm, of the right radius distal metaepiphysis measuring 28 × 25 × 20 mm (+41 HU), in the proximal right ulna measuring 27 × 20 × 16 mm, multiple lesions of bone rarefaction in the proximal right and left femurs. The DXA showed decreased BMD (Z-score L1–L4 –1.8 SD, Neck –2.3 SD, Radius 33% –5.0 SD). Sestamibi scintigraphy showed increased uptake behind the sternum with dimention of 5 cm. Parathyroidectomy was performed, the severe hungry bone syndrome with muscle twitches, impair temperature sensivity, panic attacks, loss of taste and insomnia appeared on the fifth day after with PTH level of 23 pg/ml, total calcium level of 2.38 mmol/l. The patient started taking calcium and vitamin D supplementation and anti–resorptive treatment (denosumab). Three months after parathyroidectomy hypocalcemia was detected with normal 25(OH)D level, PTH level wasn't measured. Six months later serum PTH level increased to 280.2 pg/ml with normal calcium and 25(OH)D levels. Neck ultrasound didn't show any pathological formation. 11C-methionine PET/CT scan was also negative. The control DXA showed improving of bone remodeling (Z-score L1–L4 –0.6SD, Neck 0.1SD, Radius 33% –1.7SD).

Conclusion

The classical presentation of PHPT isn't frequent nowadays because of serum calcium screening. Brown tumors appears through rapid osteoclast turnover and can significantly decreased QoL due to the multiple fragility fractures. It's likely that the patient has a reccurent PHPT, and negative imaging data requires a more detailed analysis.

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EP110

The effect of teriparatide therapy on the rate of consolidation of a leg fracture in a patient with systemic osteoporosis (description of a clinical case)

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Patient J, b. 1963 sent to an endocrinologist by a traumatologist due to the lack of consolidation of a fracture of the right ankle with complaints of pain, restriction of movements in the right ankle joint.

Medical history

09/19/2018 suffered a combined fracture of the lower leg bones when falling from a height of their own growth after falling at home falling from a height of their own growth. Reposition was performed, a circular plaster cast was applied, immobilization in a cast until 11.24.2018. Moved with crutches. 12/24/2018 repeated fall, upon examination by a traumatologist and control radiography – no fresh fracture was detected.

Conclusion unconsolidated fracture of the external ankle, partially consolidated fracture of the medial ankle and posterior edge of the right tibia from 09/19/2018 with subluxation of the foot outward. Contracture. T–score L1–L4 = –2.61 blood electrolytes – normal, PTH 34, 25 (OH) D 13.1, B–crosslaps– 0.848, P1NP 20.3, osteocalcin <2.0, calcitonin – <2.0.

MSCT 01/07/2019:

Fractures of the distal parts of the bones of the right lower leg are determined: Unconsolidated fragmentary fracture of the lateral ankle, with diastasis of bone fragments up to 5 mm. The edges of the bone fragments are uneven, sometimes sclerotic. Improperly fused fracture of the medial ankle, with diastasis in the anterior sections up to 4 mm. The edges of the fragments are clear, sclerotic, consolidation is in the posterior sections. Consolidated fragmentary fracture of the posterior edge of the tibia, with deformation of the posterior contour of the bone, without significant displacement of fragments. Paraarticular soft tissues are swollen.

Conclusion

CT picture of a three–ankle fracture of the right ankle joint. Spotted regional osteoporosis in the bones that form the right ankle joint, bones of the right foot (Zudek syndrome).

Ds: POP complicated by a pathological fracture. Vitamin D deficiency.

Treatment

Vigantol 15 drops daily – 6 weeks.

Teriparatide 20/

Rh– control 02.17.19. A consolidated fracture of the external ankle is determined. Bone callus is formed satisfactorily, post–traumatic bone deformation at this level is noted. Consolidated fracture of the medial ankle. Consolidated fracture of the posterior edge of the tibia.

02/19/19: P1NP 41.9, B–crosslaps– 1.158, 25 (OH) D 50.3, Ca, P – norm.

Conclusion

A clinical case demonstrates the acceleration of consolidation of a complex shin fracture with delayed consolidation during therapy with teriparatide.

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EP111

Bone quality is affected in acromegaly beyound insulin resistence

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Introduction

Diabetes mellitus and acromegaly are both associated with an increased risk of fracture caused by altered quality of bone. TBS represents an important tool for assessment of bone microarchitecture.

Objectives

The aim of this study is to assess the bone deterioration through the trabecular bone score (TBS) and to compare TBS and Z score between 2 groups of patients: acromegaly and diabetes mellitus.

Methods

This retrospective study included 2 groups of patients diagnosed and monitored in our clinic. 17 patients with diabetes mellitus between 45–77 years old (63.88 mean age; 32.04 mean BMI) were compared with 10 patients with acromegaly between 51–77 years old (61 mean age; 29.94 mean BMI). We selected the acromegalic patients without diabetes mellitus. In acromegalic group 3 patients had osteoporosis, 3 osteopenia and 4 had a T score in normal range while in diabetes group 3patients had osteoporosis, 2 osteopenia and 11 had a T score in normal range. The One way Anova test, used to compare TBS and Z score in the 2 groups, showed a lower mean TBS and hip Z score in acromegalic patients than in diabetic patients (1.260 vs 1.358, 95% CI, $P<0.05$ and –0.4 vs 1.22, 95% CI, $P<0.01$). Mean lumbar spine Z score didn't show any significant difference between the 2 groups. The limitation of our study is the small number of patients.

Results

Our study shows that acromegaly is associated with a lower TBS and hip Z score than diabetes mellitus which means that acromegaly represents an additional risk factor for altered bone quality, added to insulin resistance, despite the older age of diabetic patients.

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EP112

Complex supplementation with calcium and vitamins D3 and B6 can prolong effect of medical rehabilitation in patients with osteoporosis and high fracture risk

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The aim of the study was to evaluate the effect of complex food supplement with calcium and vitamins D_3 and B_6 intake on muscle strength and balance function during 1-year follow-up after rehabilitation course in patients with osteoporosis and high fracture risk

Methods

The study comprised 119 men and women aged 50–80 y.o. with established osteoporosis or high probability of major osteoporotic fracture by FRAX model initiating 3-week course of rehabilitation. 41 patients who had already received anti–resorptive therapy were included in the Studied group 1 (SG1), and 78 patients who were never previously treated with anti–osteoporotic medication were randomized in SG2 ($n=39$) or SG3 ($n=39$). The food supplement containing Vitamin D_3 30 mg, Pyridoxine Hydrochloride 4 mg, Calcium Citrate 320 mg and HDBA organic complex 400 mg in daily dosage was administered to patients in SG1 and SG2 for 12 months. Changes

in dynamometry and balance tests were assessed after 3 weeks, and in 6 and 12 months as follow–up.
Results
Achieved higher levels of muscle strength during the rehabilitation course were maintained for up to 12 months in the back extensors and flexors in SG1 and SG2, and up to 6 months in the lateral back flexors in SG1 ($P>0.05$ vs 3 weeks). The effect of medical rehabilitation completely disappeared in SG3 after 6 months ($P<0.05$ vs 3 weeks). Improved vs baseline stabilometry data in balance coefficient and pressure center deviation speed were registered in SG1 and SG2 in 6 and 12 months ($P>0.05$ vs 3 weeks). Achieved during rehabilitation positive result of balance control measured with One-leg-standing test was maintained only in SG1 for 12 months ($P>0.05$ vs 3 weeks), but it significantly ($P<0.05$) worsened in SG3 at follow-up.
Conclusion
Long–term intake of food supplements containing calcium with vitamins D_3 and B_6 can help to maintain the effect of rehabilitation on muscle strength and balance in patients with osteoporosis and a high risk of fractures.

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EP113

Zoledronic acid treatment in women with postmenopausal osteoporosis; A cohort follow–up.

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Zoledronic acid (ZA) treatment increases bone mineral density (BMD), decreases bone turnover markers and reduces the risk of fractures in patients with osteoporosis (1).
Objective
Observe and quantify the changes in BMD and bone turnover markers in postmenopausal osteoporosis (PO) patients treated annually with zoledronic acid 5 mg intravenously.
Material and methods
Medical records (MR) of PO patients whom received ZA from 2007 to 2017 were retrospective evaluated. Parametric test (paired T-test for quantitative variable) × 2 for qualitative variable were performed following variable distribution. Kaplan Meier- log rank test, lineal and cox regression were performed. SPSS and Stata14.0 software were used for statistical analysis.
Results
130 women were included

Age (years)	68.1±9.4
BMI(Kg/m^2)	25.7±5.1
Menopause age	49±5.6
Previous fracture	45.4% (n=59/130)
Vertebral fractures	47.4% (n=28/59)
Non–vertebral fractures	61% (n=36/59
Multiple fractures	30.5% (n=18/ 59)

A percentage of 50.8% had received prior treatment with oral bisphosphonates for a time period of 1.7±2.4 years, 15 patients received others previous treatments.
The major prescription for ZA was: lack of response to oral bisphosphonates 36.2% (n=47/130), very low bone mass density (T-sc<–3.5): 31.5% (n=41/130), new fracture under treatment with oral bisphosphonates: 7.7% (n=10/130), digestive intolerance to oral bisphosphonates 24.6% (n=32/130) and previous history of fx: 45.4% (n=59/130).
From total 84 patients received 2 infusions and 45 patients, 3 infusions with ZA respectively.
Adverse events were observed in 4.6% (n=8) of patients.
One year after ZA, there was a significant increase at lumbar spine(LS) BMD in 3.7% (n=0.009) and total hip (TH) 4.5% (P=0.004), however in the following years the increase was not significant in both regions. There were no significant changes in femoral neck (FN).
There was a significant decrease 49% ($P<0.001$) in C–telopeptide of type I collagen (CTX) values, but only after the first year of infusion.
Conclusions
In our cohort the annual treatment with intravenous ZA 5 mg produced a significant increase in BMD for LS and TH and a significant decrease in CTX per year. Adverse effects were uncommon. We believe that this study despite its limitations, provides useful information regarding the effectiveness and safeness of ZA as a therapeutic option for PO treatment.

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EP114

Patients characteristics with low–trauma vertebral fractures: A descriptive multi–center analysis

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Background
Vertebral fractures are the most common type of osteoporotic fractures. Prevalence of osteoporosis and osteoporotic vertebral fractures were not addressed and studied previously in the UAE. This study aims to describe for the first time the demographic and morphological characteristics of patients with fragility vertebral fractures in the UAE.
Methods
This is a retrospective medical records review of patients with low-trauma vertebral fractures from two tertiary centers during 2011–2016. Patients' gender, age at the time of fracture, nationality, BMI and the anatomical location of fracture were described.
Results
A total of 143 subjects were diagnosed with low-trauma vertebral fractures in the Emirate of Abu Dhabi during 2011–2016. Of these, 98 were women (68.5%) and 45 were men (31.5%). The overall mean age at diagnosis was 62.5. Almost half of the patients were younger than 65 years. Around 60% of the patients were UAE nationals. 51 (36.7%) patients were obese with a mean BMI of 35.3 kg/m^2. Women with vertebral fractures had statistically significant higher mean BMI compared to men (P=0.041). Nearly 40% of men had normal BMI compared to 20% of the female patients. Most of the fractures were compression fractures (77.6%) and were located in the thoracolumbar transition region.
Conclusion
Patients with vertebral fractures were predominantly females. Overweight and obesity were more prevalent specially in female patients. Male patients had lower BMI compared to females.
Keywords: Low–trauma, osteoporosis, vertebral fracture, body mass index, fragility fracture.

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EP115

Tibolone effects on bone mineral density in a patient with complete androgen insensitivity syndrome, a one year follow–up

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Background
Patients with complete androgen insensitivity syndrome (CAIS) who undergo gonadectomy have evidence of reduced bone mineral density (BMD) and perhaps, higher risk of fragility fractures. Because of this, hormonal replacement therapy (HRT), usually in the form of estrogen, is used as patients with CAIS have 46, XY genotypes having androgen receptor abnormalities making them resistant to the effects of androgen. Tibolone, a "selective tissue estrogenic activity regulator" (STEAR), is a synthetic compound with estrogenic (anti-resorptive properties) on bone, preventing bone loss, increasing BMD and preventing fractures in postmenopausal women.
Case Description
A 45-year-old phenotypic woman with no prior history of fractures presents to the clinic for evaluation of primary amenorrhea. Her subsequent evaluation was consistent with a diagnosis of CAIS. She was 171 cm in height and 67 kg in weight (BMI of 29.38 kg/m^2). Physical examination was notable for scant androgen-dependent body hair, Tanner stage V breast development, and a blind vaginal pouch. Work-up showed an absent uterus on magnetic resonance imaging, a 46, XY karyotype, and hormonal evaluations consistent with male normative ranges for total testosterone estradiol. She subsequently underwent two gonadectomies (with a 10-month interval)

which showed gonads having testicular histology. Dual-energy x-ray absorptiometry revealed osteopenia based on normal female range. Baseline spine T-score was –1.7 (0.960 g/cm^2), right total hip T-score was –1.3 (0.841 g/cm^2), right femoral neck T-score was –1.0 (0.895 g/cm^2), left total hip T-score was –1.7 (0.794 g/cm^2), left femoral neck T-score was –1.2 (0.875 g/cm^2), and 33 percent left radius T-score was –0.8 (0.809 g/cm^2). Additional workups for secondary causes of osteoporosis were unremarkable. Our patient was started on tibolone 2.5 mg daily together with calcium and vitamin D3 supplementation. After one year of treatment, spine BMD increased by 2.3%, right total hip increased by 1.7%, right femoral neck increased by 3.9%, and left femoral neck increased by 1.7%. There was no significant change in the left total hip BMD. She did not experience any adverse drug events on tibolone.
Conclusion
While the efficacy of tibolone in post-menopausal osteoporosis has been demonstrated in literature, its role in the management of post-gonadectomized patients with CAIS has not been documented. We present a patient with CAIS who had increased BMD after one year of tibolone 2.5 mg treatment. A long-term study of tibolone in this rare condition is warranted so effective treatment strategies could be offered to patients to mitigate bone loss especially during early gonadectomy.

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EP116

Indications of surgical treatment of secondary hyperparathyroidism in hemodialysis patients

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Introduction
Hyperparathyroidism is a fairly common pathology that can cause functional and vital complications. Its treatment combines a medical component and a surgical one.
The aim of this work is to specify the surgical indications for this pathology.
Materials and methods
It is a retrospective study bringing 58 cases of secondary hyperparathyroidism collected over a period of 16 years (from 2001 to 2016).
Results
Our series includes 23 women and 25 men with a sex ratio of 1.5. The average age of our patients was 43 years (17 to 78 years).
All patients had chronic renal failure at the hemodialysis stage, progressing for an average duration of 6.77 years. They received medical treatment with calcium and vitamin D.
Bone pain was the most frequent reason for consultation (100 % of cases), followed by muscle fatigue (80 % of cases) and by a pathological fracture in 2 cases.
The diagnosis of hyperparathyroidism was made in front of high PTH figures, associated with hyperphosphoremia and a tendency to hypocalcaemia. Sixty percent of patients retained hypovitaminosis D despite well-managed supplementation.
Seventy-five patients had radiographs of the hands and skull, showing diffuse bone demineralization.
Parathyroid scintigraphy associated with cervical ultrasound, requested in all patients, showed hyper fixation of the thyroid gland in regard in 95% of the cases.
A 7/8 reduction parathyroidectomy was performed in all patients with a drop of more than 50% in PTH levels in all cases.
We noted a clear improvement in functional complaints postoperatively in all patients.
Conclusion
Secondary hyperparathyroidism remains a frequent problem in chronic hemodialysis patients. Its treatment is above all preventive. Surgery is only indicated if medical treatment fails.

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EP117

Factors associated with vitamin d deficiency among adult population in carpathian region

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Background
Vitamin D deficiency is widespread in Ukraine, particularly among older adults. Factors associated with vitamin D deficiency are not well defined.
The aim of the study was to evaluate vitamin D status and its correlatation among older adults of 5 communities in Ukrainian Carpathians.
Materials and methods
This cross–sectional study was based on study data for 1254 men and women aged 20–82 years. Anthropometric and socioeconomic data were collected in June-July 2018. Serum 25(OH)D levels were detected using a chemiluminescence immunoassay. The following socioeconomic data were obtained through self–administered questionnaires: education level, lifestyle, residency, and dietary habits. A logistic regression model was used to assess associations between anthropometric factors, socioeconomic factors and serum 25(OH)D levels.
Results
Median levels of serum 25(OH)D in men and women were 21.43 and 18.47 ng/ml, respectively. Vitamin D deficiency was common in subjects involved into the study, even though data collection was conducted during summer. The general prevalence of serum 25(OH)D levels < 20 ng/ml were 41.3% and 59.2% for men and women respectively. The general prevalence of serum 25(OH)D levels < 10 ng/ml were 3.7% and 6.4% for men and women respectively. A multivariable model indicated serum 25(OH)D level ≥20 ng/ml was significantly and positively correlated with male sex, and residency by the sea. The model also indicated that high level of physical activity was a protective factor of vitamin D deficiency for men and women. By contrast, deficient serum 25(OH)D level significantly correlated with education level (lower than primary school) or obesity for all patricipants.
Conclusion
This cross-sectional study of older adults in communities in Ukraine demonstrates that key factors positively correlated with serum 25(OH)D levels ≥20 ng/ml include male sex, residency about sea level, high physical activity and education level, maintenance of normal BMI.

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EP118

Periodontitis and osteoporosis. A frequent coexistence with dangerous implications

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Periodontitis is a serious medical condition which may lead to edentulousness in middle aged patients. It is a chronic inflammatory systemic disorder which affects the oral cavity, the maxilla and mandible. It may be associated with osteoporosis. It presents unique problems in the management of osteoporosis. The patients are in the imminent danger of losing teeth. Some of the antiosteoporotic agents may induce osteonecrosis, while they may complicate the implantation of dental implants.
The aim was to describe the management of osteoporosis in patients with periodontitis.
A group of patients, 10 female and 1 male presented to the outpatient osteoporosis clinic. They had a T score of –2.8 to –3.6. They also had periodontitis. A group of 4 patients had already lost 1 to 4 teeth, and were in the process of dental implant installation. An extensive laboratory and clinical examination was performed.
Within the group of patients with osteoporosis and periodontitis, patients with osteoporosis were managed with anticatabolic treatment. The patients who were in the process of dental implant installation were managed conservatively with calcium and vitamin D until the installation of the implant was complete and a period of 3 months after installation. Thereafter, antiosteoporotic agents were administered.
Periodontitis is a chronic systemic medical disorder which affects patients in the middle age group. Postmenopausal women are particularly vulnerable. In addition, it is a systemic inflammatory disorder and may be implicated in the pathogenesis of osteoporosis. The management of osteoporosis in this group is particularly challenging. They are in danger for the development of

osteonecrosis of the jaw. Patients should be managed conservatively while in the process of dental implant installation. They should be managed with caution while care should be exercised in oral hygiene.

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EP119

Systemic inflammation in primary hyperparathyroidism

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Parathyroid hormone(PTH) is a peptide hormone that regulates ionized calcium. Primary hyperparathyroidism, in which the bone-building-destruction balance is disturbed, is due to the uncontrolled secretion of parathormone. The systemic inflammation index (SSI) is a variable that has been validated in studies aimed at evaluating the inflammation that has been frequently mentioned recently. The disruption of this bone-making destruction process affects the inflammatory process in the body. For this reason, we aimed to compare systemic inflammation index and neutrophil lymphocyte ratio in hyperparathyroidism patients before and after operation in our study.
Material and methods: In the last 5 years, 28 patients who were followed-up in the endocrinology outpatient clinic for hyperparathyroidism were included in the study. Parathormone, calcium, phosphorus, alkaline phosphatase, neutrophil, lymphocyte, and platelet values were recorded before the operation and in the 6th month of the operation. Since the normal distribution was not seen, we performed the evaluation of the results with non-parametric tests.
Results: The preoperative and postoperative alkaline phosphatase, parathormone, calcium and phosphorus values of the patients were found to be significantly different. However, although their mean values differed (Table 1), the systemic inflammation index and neutrophil-lymphocyte ratio did not differ significantly. (Table 2)

Table 1

Descriptive Statistics

Pre Post Operative		N	Minimum	Maximum	Mean	Std. Deviation
Preop	SSI	28	201,67	3820,65	683,4551	698,53979
	Neutrophil Lymphocyte Ratio	28	,93	16,19	2,8830	2,84131
	Valid N (listwise)	28				
Postop	SSI	28	178,42	998,18	494,2027	221,83034
	Neutro-philLympho-cyteRatio	28	,58	5,25	2,0761	,93910
	Valid N (listwise)	28				

Table 2

Test Statistics[a]

	*P*th (pg/ml)	Ca (mg/dl)	Alp (U/l)	*P* (mg/dl)	SSI	NLR
Preoperative (median)	256,5	11,53	129	2,11	441,09	2,07
Postoperative (median)	43,5	9,28	85,5	3,35	414,40	1,92
Asymp. Sig. (2–tailed)	,000	,000	,002	,000	,646	,325

Pre–Postoperative Statistics

Discussion
Systemic inflammation index and neutrophil lymphocyte ratio are remarkable markers in recent years. In our study, the mean of preoperative and postoperative SSI was found to be 683 and 494, respectively. Mean and median values show a postoperative decrease as we expected. However, no statistical difference was found. Insufficient number of patients can cause statistical significance. Reducing the type 2 error by expanding the number of samples will show the result of this situation.

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EP120

Persistent hyperparathyreoidism due to ectopic parathyroid gland

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Sixteen percent of parathyroid adenomas can be situated in an ectopic location. Ectopic parathyroid glands result from aberrant migration during early stages of development, and lack of successful identification may lead to lack of success in parathyroid surgery. These glands are most frequently found in the anterior mediastinum, in association with the thymus or the thyroid gland. Ectopic parathyroid glands are a major cause of persistent and recurrent hyperparathyroidism.
The aim of the study was presented to patients with persistent primary hyperparathyroidism due to ectopic parathyroid adenoma in the chest.
Case Report
This is a 67–year–old woman who was presented with fatigue and was diagnosed with primary hyperparathyroidism two years ago. At the time of diagnosis, the patient had the following findings: high levels of parathyroid hormone (PTH), ionized calcium and easily reduced phosphate values. Technetium-99m–sestamibi (MIBI) scintigraphy scan was positive and detected enlarged and hyperactive upper right parathyroid gland. The ultrasound showed a multinodally enlarged thyroid gland. The patient was referred to a surgeon. The parathyroid hormone and ionized calcium levels were not normalized postoperatively. The repeated Technetium-99m-sestamibi (MIBI) scintigraphy showed this time an enlarged and hyperactive lower left parathyroid gland. After that, an exploitative cervicotomy was done but the parathyroid glands could not be enlarged in the expected projects. Even after repeated operations there was again an elevated PTH level, elevatedionized and total calcium levels with normal calciuria. The patient was again advised to do parathyroid gland scintigraphy. The third scintigraphy detected localized parathyroid adenoma/hyperplasia in superior mediastinum (an enlarged and hyperactive parathyroid gland ectopically localized behind the upper part of the left half of the sternum manubrium).The computed tomography of the chest and lower neck showed an ovoid soft tissue density area measuring about $21 \times 18 \times 13$ mm in the superior mediastinum. The patient was again referred to the surgeon. The removal of the lesion resulted in rapid improvement in serum calcium and parathyroid hormone.
Conclusion
In addition to the enlarged and hyp\eractive parathyroid glands at the typical site of the neck, the development of ectopically located parathyroid glands is also possible. Therefore, we think that the attention should be paid to this in dailyclinical practice. The neck ultrasound and 99mTc Sestamibi scan are first–line imaging modalities, although with low sensitivity and specificity. However, their combination with modern techniques, such as single photon emission computed tomography (SPECT) alone or in combination with CT (SPECT/CT) increases their diagnostic accuracy.

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EP121

Teriparatide in the treatment of severe osteoporosis: Results of a case series

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Introduction
Known as a potent anabolic drug, teriparatide has a stimulating effect on bone formation, increasing bone mineral density (BMD) and reducing fracture risk.
Methods
11 Caucasian women (mean age 66 years old) with severe osteoporosis treated with recombinant human parathyroid hormone (1–34) – teriparatide (Forsteo) 20 micrograms daily for 24 months were added to the study.
BMD at lumbar spine, total hip and femoral neck was measured before treatment (baseline), 12 and 24 months after initiation using dual energy x-ray absorptiometry (DXA GE Lunar). Two patients had plate osteosynthesis material at lumbar spine so DXA was performed only at total hip and femoral neck. All patients had fragility fractures, diagnosed with radiography/ vertebral MRI/ VFA: 3/11 had one vertebral fracture, 6/11 multiple vertebral fractures, 3/11 forearm fractures, 3/11 femoral fractures (one bilateral), 1/11 patella fracture and 1/11 had a pelvic fracture.
One patient had postpartum BMD below the expected range for age and vertebral fractures. 7/11 patients had previous anti–osteoporosis treatment. After 24 months of teriparatide, 10/11 patients started ibandronate 3 mg iv every 3 months, 1/11 started denosumab 60 mg sc every six months.
All received daily supplements of 500–1000 mg of calcium and 1000–2000 IU of Vitamin D. We measured osteocalcin (OC) at baseline, 12 and 24 months after initiation. We determined changes in percentage of BMD and serum OC in 12 and 24 months compared to baseline.
Results
Treatment with teriparatide determined an increase in BMD of total hip after 12 months (+ 2.18%) and significant increase after 24 months (+ 3.53%). The BMD changes at the femoral neck were 5.32% at 12 months and 3.15% after 24 months. The most significant increase in BMD was found at lumbar spine: 9.08% after 12 months and 8.36% after 24 months compared to baseline. The increase in OC was 90.47% after 12 months and 40.4 % after 24 months of teriparatide. The patient with postpartum BMD below expected for age had an important increase in BMD at lumbar spine after 12 months of 16.45% and of 24.1% after 24 months.
Treatment was well tolerated, and no serious side effects were observed.
No new fractures were diagnosed during treatment.
Conclusion
Our study suggests that teriparatide has an effective osteoanabolic effect and it is safe and well tolerated. Prolongation of follow–up is needed to see the evolution of BMD on patient treated with antiresorptive agents following teriparatide.

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EP122

Failure of parathyroidectomy or PTH rebound in primary hyperparathyroidim

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Introduction
Juvenile primary hyperparathyroidism represents more severe form of the disease, often with organ damages. Genetic mutation and paarthyroid hyperplasia are more frequent than in adults.
Case Report
20–year–old patient with familial history of kidney stone. She was hospitalized for major hypercalcemia at 3.65 mmol/l (2.2–2.6 mmol/l) discovered on daily chronic vomiting and alteration of the general condition. The biological balance was in favour of primary hyperparathyroidism with hypophosphoremia at 0.58 mml/l (0.85–1.5 mmol/l) ; hypercalciuria at 7.8 mmol/24 h (2.5–7.5 mmol/24 h), PTH at 1050 ng/l (15–60 ng/ml), Vit D at 7ng/l (30–100 ng/ml).
The morphological assessment is as follows:
–parathyroid sesta MIBI scintigraphy and cervical ultrasound were compatible with a left P3 inferior adenoma measuring 33–14–13 mm
Treatment with mimpara was instaured without success. Thus, left lower parathyroidectomy for adenoma by cervicotomy was performed, without exploration of other sites
Anatomopathology concluded to parathyroid main cell adenomas, without signs of malignancy.

	21/10/2019	24/11/2019	Surgery 2/12/2019	3/12/2019	4/12/2019	5/12/2019	6/12/2019	10/1/2020
Calcémie (mmol/l)	2.83	3.4	2.93	2.77	2.6			2.17
NV(2.2–2.6)								
PTH (ng/l)	1643	599	73		6.9	20.9	63	96
NV (15–60)								
PTH (ng/l) itraoperative			1133					

Genetic research (multiple endocrine neoplasia and Ca SR mutation were performed (results unavailable). we completed with a statistical pituitary assessment (prolactin, FT4, TSH, GH, IGF1) plasma DM) and hormonal assessment (glucagon, somatostatin, VIP) wich were normal.
Discussion
Calcemia is still normal 1 month after operation at 2.17 mmol/l . However the rapid reascension of PTH to 182 pg/ml is considered to be quite normal since it is a post–operative rebound effect linked to both the resumption of function of other parathyroids and probably increased by vitamin D deficiency despite adequate supplementation. But we may fear an hyperplasia of parathyroids and it is the genetic study and the evolution of calcemia and PTH that will predict the etiology of this hyperparathyroidism.
Conclusion
Genetic study in young patients with primary hyperthyroidism is essential given the higher risk of recurrence in familial forms. The level of calcimia may sometimes drive the time of surgery.

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EP123

Severe, symptomatic hypocalcemia due to denosumab and vitamin d deficiency in a post–menopausal female with osteopenia

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Denosumab is a monoclonal antibody used in the treatment of osteoporosis to prevent bony injuries by increasing bone density. It does so by binding to RANK-L, which is then unable to activate RANK, thereby preventing osteoclast maturation and viability. Although rare, the effect of denosumab can interfere with the body's calcium homeostasis and lead to a hypocalcemic state. We present a case where a post-menopausal female developed severe, symptomatic hypocalcemia from a multifactorial etiology of a side effect from denosumab and concomitant Vitamin D Deficiency. The patient originally presented to the ED with a chief complaint of intermittent and worsening whole body numbness and confusion per her family members. Her serum calcium level on presentation was 4.3 mg/dl and attempts at improvement were refractory to multiple administrations of intravenous calcium; however, her symptoms and calcium levels improved after receiving continuous intravenous calcium and Vitamin D later during her hospital stay. Importantly, this condition could have been prevented as she was not a candidate for denosumab therapy given the results of her most recent bone scan. This case allows for insight on use of denosumab and which patients are optimal candidates for the drug and who are not, as well as the necessary testing and diagnoses to establish before initiating treatment with the drug.

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Diabetes, Obesity, Metabolism and Nutrition

EP124

The effect of PCSK9 Inhibitor EVOLOCUMAB on aldosterone among high cardiovascular risk patients

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Background
Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors decrease the degradation of low–density lipoprotein (LDL) receptors, thereby increasing the removal of LDL particles from the blood and significantly reducing LDL cholesterol levels by an average of 65%. Blom et al. showed

changes in vitamin E, adrenocorticotropic hormone (ACTH), cortisol, total testosterone, and estradiol in EVOLOCUMAB (PCSK9 inhibitor)–treated patients [1]. There are currently no published data on the impact of PCSK9 inhibitor monotherapy on aldosterone.
Aim of the study
To examine the effect of EVOLOCUMAB monotherapy on LDL cholesterol reduction and steroidogenesis in high cardiovascular risk patients with statin intolerance.
Methods
Lipid profile, sodium, potassium, aldosterone, cortisol, and ACTH were analyzed at baseline and after 3 months of EVOLOCUMAB therapy. Each participant underwent two dynamic tests, a 250 mg ACTH test and an ambulation test, on two consecutive days at the beginning and end of the study.
Results
Fifteen patients were included in the study. Total cholesterol, LDL cholesterol, lipoprotein (a), and stimulated aldosterone levels were significantly lower after 3 months of EVOLOCUMAB therapy. There were no significant changes in ACTH, cortisol, or potassium levels.
Conclusions
Reduction in stimulated aldosterone secretion by EVOLOCUMAB treatment could theoretically be associated with the reduction of cardiovascular events, and that possibility warrants further investigation.
Reference:
1. Blom DJ, Djedjos CS, Monsalvo ML, Bridges I, Wasserman SM, Scott R, Roth E. Effects of Evolocumab on Vitamin E and Steroid Hormone Levels Results From the 52–Week, Phase 3, Double-Blind, Randomized, Placebo–Controlled DESCARTES Study. *Circ Res*. 2015 Sep 25 **117(8)** 731–41.
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EP125

Therapeutic inertia in lipid management of diabetic patients in secondary prevention

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Introduction
Dyslipidemia (DL) in diabetic patients is frequently undertreated. Even when cLDL targets have not been met, treatment remains unchanged despite the availability of alternatives approaches. This is known as therapeutic inertia (TI).The aim of this study was to evaluate the prevalence of TI in lipid management among diabetic patients and to analyse associated factors and possible causes.
Material and methods
Retrospective, cross-sectional study. Diabetic patients in secondary prevention followed up in an Endocrinology outpatient clinic, from January to June 2019. All with suboptimal cLDL levels: >70 mg/dl, according to ESC/EAS 2016 guidelines for the management of dyslipidemias. TI was considered when a lipid–lowering agent was not changed or added. Results in mean (Standard Deviation). Bivariate analysis: Pearson chi*square/Student *t* test.
Results
78 patients. 61.5% men. Age 72.2 (10) years, duration of diabetes: 16.3 (10.5) years. 94.9% DM 2. Weight 76.2 (14) kg, BMI 28.2 (4.7) kg/m^2. Mean HbA1c 8 (1.5)%, cLDL 98.5 (25.5) mg/dl, glomerular filtration rate 69.2 (24.7) ml/min. Number of chronic treatments: 10.7 (4). Complications and comorbidities: 56.4% ischemic cardiopathy (IC), 29.5% stroke, 28.6% peripheral artery disease (PAD), 23.6% diabetic nefropathy, 20.8% diabetic retinopathy (DR) and 11.5% diabetic neuropathy (DN). 29.5% with renal insufficiency and 9% with hepatopathy. Cognitive impairment in 6.4%.Type of statin: high potency in 38.8%, low-intermediate potency in 62.2%.14% without any statin. Only 10.7% received the maximum dose of statin. In 5.3% statin intolerance was reported.
cLDL levels were higher in women, hepatopathy, patients taking less than 5 chronic treatments and without statin($P<0.05$).There were no differences depending on age, renal insufficiency, cognitive impairment, HbA1c, statin intolerance, maximum dose of statin and the presence of hypertension, IC and PAD.
TI was observed in 80.7% of patients. It was not modified based on age, duration of diabetes, renal insufficiency, hepatopathy, cognitive impairment, number of chronic treatments nor number of changes in regular treatments. There were also no differences depending on other cardiovascular risk factors and type of vascular disease: tobacco, hypertension, IC, stroke, DN, PAD nor DR.
We observed less TI associated with higher cLDL and lower HbA1c levels ($P<0.05$).
Conclusions
TI was common in the lipid management of diabetic patients. We found higher cLDL and lower HbA1c levels as factors that influenced in TI, this could be due to a sequential treatment, optimizing the treatment of DL after an adequate glycemic control. The better management should be an integrated treatment of all cardiovascular risk factors.
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EP126

Augmentation index in the assessment of pulse wave reflection assessment in lean and obese women with polycystic ovary syndrome (PCOS)

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Objective
Conflicting findings have been published regarding the pressure wave reflection and the arterial stiffness in young women with PCOS as opposed to the overt *ab initio* presence of endothelial dysfunction compared with controls which can be reversed six months after metformin administration. The aim of this study was to investigate arterial stiffness and wave reflections in young women with polycystic ovary syndrome (PCOS) with respects to the different weight and to evaluate the effect of metformin treatment on the aforementioned indices.
Methods
Sixty–four young women, 35 with PCOS (P) (20 lean (L), PL; 15 overweight/obese (O_{WB}), $P_{OW/OB}$) and 29 (18CL; 11 C_{OWB}) normal women were studied. Wave reflectionwas studied by the Augmentation Index (AI) as central augmentation pressure–to–pulse height ratio at heart rate (HR) 75 (C_AGPH_HR75) or without HR correctionC_AGPH and the central augmentation time index (C_ATI), bpm and biochemically by advanced glycated end–products (AGEs). Endothelial function was studied biochemically byplasma endothelin 1 (ET–1) levels. The metabolic and hormonal profile was assessed. Metformin (1700 mg daily) was administered for six months in 20 (9 lean and 11 obese) women with PCOS and the above evaluations were repeated.
Results
There was no significant difference in age among the two groups. Wave reflection sindices did not differ between PCOS and controls, but C_AGPH_HR75 significantly improved post–metformin treatment in POW/OB ($P=0.046$). AGEs differed between PCOS women groups and controls groups ($P<0.001$) but their values did not normalize after metformin treatment. Testosterone levels were higher in PCOS compared to control women and MATSUDA index values were lower in PCOS compared to control women but without normalization of their values post–metformin treatment. ET–1 levels did not differ between PCOS and controls, but significantly improved post–metformin treatment in both lean and obese PCOS groups ($P=0.01$ and $P=0.04$, respectively).
Conclusions
Wave reflections markers seem to be a covert negative predictor in PCOS but that ameliorate post–metformin treatment particularly in overweight/obese PCOS women.
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EP127

Hyperuricemia in type 2 diabetes patients with atherosclerotic cardiovascular diseases.

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Background
Studies show relationship between serum uric acid (SUA) and such diseases as type 2 diabetes (T2DM), hypertension (HT) and atherosclerotic cardiovascular disease (ASCVD). There is relationship both in hyperuricemia (HU), and high–normal values of SUA. Significance of this association is unknown; there are controversial data concerning HU role in patients with T2DM/CVD.
The aim of the study was to assess SUA in T2DM patients with ASCVD.
Method
Participants were 82 hypertensive T2DM patients, treated for HT or CVD; 52 patients had established ASCVD: CAD (previous myocardial infarction/MI, or/and PCI, CABG), peripheral artery disease/PAD (ankle–brachial index < 0.9), or/and stroke (by MRI-data). At entry 83% were receiving hypotensive drugs (one or more), half of them weren't treated adequately. Statins were used in 61 patient. Participants were divided into 2 groups (Gr). G.r.1, 52 patients with ASCVD (mean age 60.1 ± 7.5yrs, 39men/13women: 35 with CAD (23 – after MI; 21 – after PCI; 11 – after GABG); 14 – with PAD (four PAD + CAD); 13 – after stroke (3 PAD + CAD). Gr.2: 30 hypertensive patients without ASCVD (mean age 58.8 ± 8.4yrs, 22men/8women). Diabetes duration (DD), SUA, HbA1c, LDL-cholesterol, triglyceride, systolic/diastolic blood pressure (SBP/DBP), body mass index (BMI) were assessed.
Results
SUA was higher, (5.77 ± 0.61 vs 4.02 ± 0.53, $P = 0.033$); DD longer (11.95 ± 2.3 vs 6.1 ± 1.8 yrs, $P = 0.04$); SBP higher (152 ± 5.3 vs 137 ± 4.9 mmHg, $P = 0.04$), and BMI was higher (33.9 ± 2.3 vs 27.4 ± 2.1, $P = 0.04$) in Gr.1 compared to Gr.2. There was not statistically significant difference in DBP (84.5 ± 6.3 vs 81.3 ± 5.1 mmHg, $P = 0.69$), HbA1c (8.3 ± 1.02 vs 8.6 ± 0.9%, $P = 0.8$); LDL–cholesterol (2.57 ± 1.09 vs 2.31 ± 1.1 mmol/dl, $P = 0.867$) and triglycerides (2.04 ± 0.8 vs 1.91 ± 0.7 mmol/l, $P = 0.902$) between two groups. BMI was higher in Gr.1 compared to Gr.2.(33.9 ± 2.3 vs 27.4 ± 2.1, $P = 0.04$).
Conclusion
T2DM + ASCVD patients have higher SUA compared to Gr.2, ASCVD patients were more hypertensive, obese and had longer DD . Further studies are necessary to assess significance of SUA as an independent risk-factor for ASCVD development in T2DM.

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EP128

Asthma control and quality of life in greek patients with metabolic disorders. Results from BOREAS study

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Introduction
Asthma is often associated with various comorbidities, which may affect its clinical intensity and severity. The mechanisms of adult–onset asthma may include several metabolic and inflammatory components that are common to the other diseases such as obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM), cardiovascular diseases and psychiatric diseases.
Objectives
Assessment of asthma symptom control and QoL in a subgroup of asthmatic patients with metabolic disorders (MD) residing in Greece, who were treated for 6 months with a Fixed Dose Combination (FDC) of Budesonide/Formoterol (Elpenhaler).
Methods
Multicenter, prospective, non–interventional, observational study (NCT03033758) of 1, 230 asthmatic patients, not previously treated with FDC ICS/LABA, from whom 1, 028 (83.6%) had not any MD. A subgroup of 199 patients (16.2%) with MD (i.e. obesity, type 2 diabetes mellitus (T2DM) and dyslipidaemia) among other comorbidities, was evaluated for asthma control and QoL using validated Greek versions of Asthma Control Questionnaire (ACQ) and Mini Asthma Quality of Life Questionnaire (MiniAQLQ), respectively.
Results
At baseline, the median (IQR) ACQ and MiniAQLQ score were 2.45 (1.71, 3.14) and 4.21 (3.47, 5.07) for the group of patients with MD whereas the median (IQR) ACQ and MiniAQLQ score were 2.13 (1.43, 2.71) and 4.65 (4.00, 5.47) for the group of patients without MD. After 6 months, we noticed a significant decrease in ACQ score ($Z = -11.450$, $P < 0.001$), a significant increase in MiniAQLQ score ($Z = -11.776$, $P < 0.001$) and a significant, strong, negative, linear correlation between the change in ACQ (–1.61) and MiniAQLQ (1.93) scores ($rs = -0.76$, $P < 0.001$) among visits for the group of patients with MD. In the group of patients without MD, similar results were observed.
Conclusions
At baseline, asthmatic patients with MD and especially obese patients and those who had T2DM, were less controlled and had worse QoL than patients without MD. Six months of treatment with FDC Budesonide/Formoterol, Elpenhaler resulted in a significant improvement both in asthma control and QoL in these two groups of patients.

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EP129

Anthropometric and body composition indices are not predictive of cardiovascular biomarkers and estimated risk in patients with type 2 diabetes on oral antidiabetic treatment

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Aims
To explore the correlations of BMI, waist circumference (WC), waist–to–height ratio (WHtR), waist–to–hip ratio (WHR) and body composition with levels of assymetric dymethylarginine (ADMA), endothelin 1(ET–1), N–terminal brain natriuretic pro–peptide (NT–proBNP), uric acid and calculated cardiovascular risks.
Methods
102 women and 67 men with type 2 diabetes on oral antidiabetic drugs participated. Serum levels of NT–proBNP were measured by electro–hemi–luminescence (Elecsys 2010, Roche Diagnostics) while enzymatic immunoassays were used for ADMA (BioVendor) and ET–1 (IBL International GmbH). Cardiovascular risks were calculated using the Framingham Risk Score (FRS), the UKPDS 2.0 and the ADVANCE risk engines. Statistical analysis was performed on an IBM SPSS 19.0 (SPSS Corp., Chicago, IL).
Results
The BMI outperformed all other indices of obesity (the WC, WHtR, WHR), as well as body composition parameters (BF%, FM, FFM and TBW) in relation to the estimated risks for CHD and stroke based on different calculators. The correlations of the obesity indices with the serum CV biomarkers were not significant except for BMI and FM vs ET–1, and for FFM and TBW vs ADMA. The correlations with serum UA were very weak.
Conclusions
The WC, WHR, WHtR, BF%, FM and FFM do apparently not add significant information related to the levels of markers of endothelial dysfunction and vascular damage or the calculated CV–risks.

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EP130

Similar effect of tocilizumab, an interleukin-6 receptor antagonist, administered either intravenously or subcutaneously on lipid levels in rheumatoid arthritis

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Tocilizumab is an interleukin-6 receptor antagonist used in the treatment of rheumatoid arthritis (RA). It is known to induce remission and inhibit radiographic progression in RA. Tocilizumab may be administered either intravenously or subcutaneously. Its effect on lipid levels and the cardiovascular risk has not been fully investigated. The aim was to study the effect of tocilizumab administered either iv or sc on disease activity, lipid levels and cardiovascular risk in RA patients.

Tocilizumab was administered iv 8 mg/kg/ 4wks (maximum dose 800 mg) in 35 patients with RA for a period of 52 weeks. Tocilizumab was administered sc 162 mg/wk in 70 patients with RA for 52 weeks. Inflammation indices, ESR and CRP and lipid levels were measured before and 52 weeks after tocilizumab administration. The DAS 28 disease activity index was also calculated.
Inflammation indices ESR and CRP decreased significantly ($P<0.001$) after tocilizumab administration in both the iv and sc groups. The DAS 28 disease activity index decreased after tocilizumab ($P<0.001$) in both groups. Total cholesterol and HDL cholesterol increased ($P<0.001$) after tocilizumab administration, LDL cholesterol and triglyceride levels also increased in both the iv and sc groups ($P<0.001$). No acute cardiovascular events were recorded during the study or thereafter in the long–term follow–up of the patients. Tocilizumab administered either iv or sc in patients with RA was shown to decrease inflammation indices and disease activity. Lipid levels increased significantly. However, total cholesterol increased in parallel with HDL cholesterol. Cardiovascular events were not observed during the study period or in the long– term follow–up of the patients. It appears that tocilizumab may be accompanied by lipid level alterations, cardiovascular risk not increasing as the adverse effects of total cholesterol may be counteracted by HDL cholesterol.

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EP131

Risk of diabetes mellitus type 2 and complications associations with atherosclerosis in the population of belarus under 40 years old

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Introduction
T2DM prevalence in Belarus is 3.489.5 per 100 thousand people, annual growth rate is 5–6%. STEPS study: in 2016–2017 the following risk factors prevailed: overweight and obesity (61.2%), dyslipidemia (36%), hypertension (50%); inactive lifestyle (78.2%). The study aim was to assess risk factors for metabolic disorders in a young healthy population. Objective. 253 people were examined: 22.1% of men and 77.9% of women under 40. Methods: We performed anthropometric measurements, determined glycemia and total cholesterol levels; 10–year risk of developing T2DM was assessed according to the FINDRISK scale, and 10–year fatal risk of events associated with atherosclerosis – according to the SCORE scale.
Results
Median age was 30 (24; 34), BMI – 23.7 (20.4; 26.6), systolic blood pressure – (115±14), diastolic blood pressure – (77±11) mmHg, point on the FINDRISK scale – 5 (2; 8), a very high 10–year risk of T2DM was not obtained, high – in 5.6% of women, interim – in 22.2% of women and 16.7% of men, moderate – in 5.6% of women and 16.7% of men, low – in 66.6% of women and men. Statistically significant association of risk factors for T2DM and atherosclerosis depending on gender, blood pressure, or total cholesterol was not obtained. We noted a significant correlation of the risk of T2DM with BMI ($rs=0.82$; $P<0.05$), with total cholesterol ($rs=0.77$; $P<0.05$) and glycemia ($rs=0.42$; $rs.05$). Direct significant correlation was also obtained for the visceral adiposity index: $0.77 \times$ TCHOL (CM) - 0.46 $\times$ BMI (kg/m^2) – 5.82 (model $P=0.000002$) with a risk level according to FINDRISK scale ($rs=0.71$; $P<0.05$) and glycemia ($rs=0.45$; $P<0.05$).
Conclusion
In people under 40 with no risk of fatal complications associated with atherosclerosis, there is a number of factors indicating a risk of T2DM, which should be taken into account at forming different risk groups for prevention.

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EP132

Variability in the distribution of epicardial fat in young patients with type 1 diabetes

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Aim
To study the distribution of epicardial fat in young people with type 1 diabetes mellitus using magnetic resonance imaging (MRI) technologies.
Material and methods
60 patients (29 men, 31 women), aged 18 to 36 years old, with an experience of type 1 diabetes from 5 to 16 years old were underwent contrastive cardio MRI. Measurements of epicardial fat (EF) were carried out on basal (B), medium (M), apical (A) segments of the left (LV) and right ventricles (RV) on a 4-chamber views.
Results
The results are presented as median and interquartile range (Q25–Q75): EFBLV – 1 [0;1] mm; EFMLV – 1 [0.1] mm; EFALV–– 2 [1.3] mm; EFBRV – 2 [1.75;3] mm; EFMRV – 2 [1.3] mm; EFARV – 2 [1.3] mm. The thickness of epicardial fat is greater in the RV (50 patients – 83.3%), however this pattern is not observed in all subjects, in 8 (13.3%) patients with type 1 diabetes the thickness of EF of ventricles were equivalent and in 2 patients (3.3%) EF is thicker in the LV.
Conclusion
The variability of epicardial fat in young patients with type 1 diabetes requires further research and comparison with the data of the morphofunctional state in the myocardium.

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Relationship between circulating netrin -1 levels, obesity, prediabetes and newly diagnosed type 2 diabetes

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Aim
Netrin is classically recognized as a neural guidance cue that has been involved in various tissues including pancreas development. Because of Netrin's tissue regenerative, angiogenic, and inflammatory suppression properties it could play a crucial role in the development of insulin resistance and type 2 diabetes. The aim of the current study is to investigate the relation between circulating levels of Netrin-1 and the glucose continuum.
Methods
Netrin-1 level was determined using a commercially available human enzyme-linked immune sorbent assay (ELISA) kit. The homeostasis model assessment of insulin resistance (HOMA-IR) was used as an index to measure insulin resistance. The sample consisted of 163 patients with mean age 52.5±11.3 years, divided in three age and BMI matched groups-obesity without carbohydrate disturbances, prediabetes and diabetes. The control group consisted of 42 healthy individuals.
Results
The Netrin-1 levels were significantly lower in patients with obesity, prediabetes and newly diagnosed diabetes compared to the control group (0.12±0.04 vs 0.19±0.07; 0.13±0.04 vs 0.19±0.07; 0.13±0.05 vs 0.19±0.07; $P<0.001$). Logistic regression analysis showed that the level of netrin–1 were negatively correlated with LDL, TG, GGT and visceral adiposity tissue.
Conclusion
The levels of Netrin-1 were decreased in patients with obesity and carbohydrate disturbances. Further studies will shed light on the role of the biomarker in development of type 2 diabetes and its complications.
Funding
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EP134

Hyperlactatemia in critically ill patients

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Objective
The aim of the study is to describe the prevalence of hyperlactatemia and changes in lactate concentrations in critically ill patients, and the associated mortality.
Materials and methods
The study included 70 patients treated in the Medical Intensive Care Unit at the Clinical Center, University of Sarajevo, in a 6–month period. The following data were obtained: age, gender, reason for admission, Simplified Acute Physiology Score II, Acute Physiology and Chronic Health Evaluation, lactate concentrations upon admission, after 24 and 48 hours, and outcome.
Results
Hyperlactatemia upon admission was present in 91.4% patients with mean lactate concentrations of 4.13±1.21 mmol/l. Lactate concentration at 48 hours was independently associated with increased in–hospital mortality ($P=0.018$). Lactate concentration after 48 h represents a statistically significant predictive marker of fatal outcome in patients (AUC 0.874, CI 0.769–0.980 $P=0.001$) with a cut off value of 2.25 mmol/l, and sensitivity of 72.2% and specificity of 92.1 %.
Conclusion
Persistent hyperlactatemia is associated with adverse outcome in critically ill patients. Lactate concentration at 48 hours is independently associated with increased in-hospital mortality and it represents a statistically significant predictive marker of fatal outcomes of patients. Blood lactate concentrations > 2.25 mmol/l can be used by clinicians to identify patients at higher risk of death.
Keywords: hyperlactatemia, critical illness.
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EP135

Comparison of two different dietetic approaches in obese and overweight patients with type 2 diabetes mellitus

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Context
Weight reduction in obese patients with type 2 diabetes mellitus (T2DM) leads to hyperglycaemia improvement and reduces complications. Thus it is important to investigate the potential benefits of the use of different dietetic approaches on weight loss.
Objective
To examine the efficacy of two different dieting methods on weight loss in patients with T2DM.
Materials and methods
30 participants with T2DM, 18 men and 12 women, overweight or obese, aged 50.8±11.2y were categorized into two intervention groups: 1rst group ($n=15$) received a diet based on equivalent exchange list food choices (EEL) and 2nd group ($n=15$) received a point–calorie and starch equivalent system (PCS) for a 39month period. The EEL diet included carbohydrate specific pre–planned meals that the subject had to follow. The PCS diet was a free food choice system, with specific points and starch content attributed to foods listed. Subjects had individual point and starch limit daily. The recommended energy consumption was 500 Kcal less than the predicted total energy expenditure. The efficacy of each method was assessed by weight loss (weight day 0– weight day 90) and % weight loss (weight day 0– weight day 90/weight day 0 × 100). Changes in body mass index (BMI) and waist circumference (WC) were also measured.
Results
Baseline BMI was 37.0±6.5 kg/m^2 for the EEL and 40.1±11.1 for the PCS group ($P=0.3$), mean weight and WC was 108.1±22.9 and 117.8±33.6 kg ($P=0.2$) and 122.6±1.4 and 117.7±24.4 cm ($P=0.5$) for the EEL and PCS respectively. At 3-months the mean BMI was 34.3±5.4 kg/m^2 for the EEL and 37.4±10.7 for the PCS group ($P=0.3$), the mean weight was 99.9±17.4 and 109.7±32.4 kg ($P=0.3$) and the mean WC was 115.9±17.7 and 111.1±20.8 cm respectively ($P=0.7$). The mean BMI reduction was 2.7±1.9 kg/m^2 for the EEL ($P=0.001$) and 2.7±1.1 for the PCS group ($P=0.0001$). Mean weight loss for the EEL was 8.1±6.7 kg ($P=0.001$) and 8.1±3.2 kg ($P=0.001$) for the PCS group. Mean WC reduction for the EEL group was 6.6±4.8 cm ($P=0.001$) and for the PCS group 6.2±2.6 cm ($P=0.001$). At 3 months %BMI reduction in EEL and PCS groups (7.0%±3.9%– 7.1%±2.9%), %weight loss (7.0%±3.9%– 7.1%±2.9%), and %WC reduction (5.3%±3.6%– 5.3%±3.6%) were not significantly different.
Conclusion:
These preliminary findings suggest that both nutritional interventions were equally effective in weight loss in patients with T2DM. More participants and longer studies are needed for safer conclusions.
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EP136

Weight gain, but not macro–nutrient intake, modifies the effect of dietary branch chain amino acids on the risk of metabolic syndrome

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Background
The aim of this study was to investigate whether both weight change and the background intakes of macronutrients modulate the association between dietary branch chain amino acids (BCAAs) and the risk of metabolic syndrome (MetS).
Methods
This prospective study was conducted within the framework of the Tehran Lipid and Glucose Study. BCAA intakes were collected using a valid and reliable semi-quantitative food frequency questionnaire. MetS components were defined according to the modified national Cholesterol Education Program Adult Treatment Panel III. Weight change was categorized as weight gain (≥ or < 7 % over 8.9 year follow -up). Dietary fat and carbohydrate intake were categorized as above/below the median intake.
Results
Among participants with weight gain ≥ 7 % during follow–up, intakes of both dietary BCAAs and its various sources (below or above the median intake) were associated with higher risk of MetS, compared with subjects with lower intakes of BCAAs and weight change ≤ 7 %. Background dietary fat and carbohydrate did not modify the association of dietary BCAAs and its various sources with the risk of MetS.
Conclusions
Weight change, but not dietary macronutrient intake, modulates the association between dietary BCAAs and risk of MetS among adults.
Keywords: BCAA, metabolic syndrome, weight change, macronutrients, interaction.
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EP137

New microbiological markers of various types of obesity (pilot study)

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Obesity is a polyetiological and incompletely studied disease. Recent publications link the special composition of the gut microbiota not only with obesity, but also with its metabolic profile[1, 2]. To study the characteristics of the gut microbiota in patients with different phenotypes of obesity, 37 patients were examined. In addition to determining the quantitative composition of the gut microbiota by the Real-time PCR method, all participants were determined by lipid and carbohydrate metabolism and 3 groups were identified according to Wildman's criteria: 1 group ($n=11$) - healthy people without obesity and overweight, 2 group($n=13$) - patients with metabolically healthy obesity (MHO), group 3 ($n=13$) - patients with metabolically unhealthy obesity (MUHO). The results showed that the differences between the 1st group without obesity and the 2nd group with MHO is in the registration in the feces of Klebsiella spp. and Proteus spp. in amounts exceeding the formal regulatory in patients of group 2. The most significant changes were obtained in group 3 (MUHO): C.difficile was detected, a significant ($P=0.05$) decrease in F.prausnitzii and an increase ($P=0.05$) in the detection frequency of banal E.coli and a more diverse composition of gut microbiota. The data obtained as a result of our pilot study revealed compositional changes in the gut microbiota among the studied groups, which could potentially be either the cause and / or display different phenotypes of obesity. It is planned to continue further study of the composition of the microbiota of the colon in patients with various phenotypes of obesity, with

only a large number of examined in groups to obtain confirmation of the identified changes in the pilot study.

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EP138

Adipokines vaspin and omentin as risk markers of disorders of carbohydrate metabolism development in overweight and obese patients

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Adipokine omentin is a connecting link between obesity and type 2 diabetes mellitus. It modulates insulin sensitivity of peripheral tissues and its secretion may change in the developed inflammation of adipose tissue at its excessive accumulation. Chemokine fractalkine is a marker of the development of inflammatory processes in the body. Objective: omentin and fractalkine contents in blood circulation depending on the degree if adipose tissue accumulation, waist circumference, blood insulin level and HOMA–IR in representatives of Ukrainian population.

Materials and methods

250 individuals aged (65.48±11.86) years were examined, their waist circumferences were measured, adipose tissue mass was assessed by bio impedance method, including relatively to the total body mass; by immune enzyme method contents of insulin, fractalkine and omentin in circulation were determined; HOMA-IR index was determined.

Results

It was revealed that blood fractalkine and omentin levels show negative correlation between them (r=–0.863, P<0.001). Blood fractalkine level correlates positively with adipose mass of the body (r=0.5341, (P<0.001)); waist circumference – (r=0.4542, (P <0.001); insulinemia and HOMA–IP levels: (r=0.7798, (P<0.001) and r=0.745, (P<0.001)). Blood fractalkine level (ng/ml)=[407.478+57.1702 × HOMA-IR+2.2580 × waist circumference]; R_2=0.626; F=273.85; P<0.00001). Omentin level correlates negatively with adipose body mass (r=–0.609, (P<0.001)); waist circumference – (r=–0.397, (P<0.001); insulinemia and HOMA–IR levels: (r=–0.799, (P<0.001) and r=–0.7706, (P <0.001)). Blood omentin level (ng/ml)=[618.3103 – 25.6928 × HOMA–IR – 2.9962 × adipose tissue mass / total body mass]; (R_2=0.676; F=339.89; P<0.00001). It was proved that accumulation of adipose mass more than 25 % of the total body mass determines growth of fractalkine level up to 750 ng/ml and over; HOMA-IR>2.77, decreased level of omentin to 500 ng/ml and less. Contents of adipose tissue more than 34 % of total body mass determine increased fractalkine levels up to 900 ng/m. and more; HOMA–IR>4.00, decreased level of omenton to 400 ng/ml and lower.

Conclusion

Important role of fractalkine and omentin in pathogenesis of diabetes mellitus in obesity was proved. The correlation was established between the adipose tissue accumulation, changes in its endocrine function, development of inflammatory processes in the body, abdominal obesity, insulin resistance and type 2 diabetes mellitus onset.

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Autoimmune diseases associated with T1D

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Introduction

Type 1 diabetes can be associated with one or more other autoimmune pathologies in case of predisposing immune background.

The aim of our study was to research the autoimmune pathologies associated with type 1 diabetes and to describe the clinical and biological characteristics of this population.

Patients and methods

This is a retrospective descriptive study including 26 patients with type 1 diabetes with at least one autoimmune pathology associated with diabetes.

Results

The average age was 35.7±8.6 years. The sex ratio was 0.23. Diabetes had evolved for an average of 17.4±6.8 years. The average body mass index (BMI) was 28.2±3.2 kg/m^2. The average HbA1C was 9.1±2.2%. The average creatinine clearance was 99.2±12.3 ml/min (CKD–EPI). The most widely described degenerative complication was retinopathy (28.1%). Hashimoto's thyroiditis was the autoimmune disease most associated with diabetes (73%) followed by celiac disease (19.2%). Only one cas of vitiligo and another case of Biermer's anemia had been found. All cases of thyroiditis were diagnosed after diabetes, as was the case with Biermer's disease. Vitiligo preceded the diagnosis of diabetes. Celiac disease preceded diabetes in the majority of cases.

Conclusion

The frequent association of autoimmune pathologies with diabetes encourages them to be screened regularly so that they are managed on time.

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EP140

Awareness of patients with type 2 diabetes about their disease

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Background

Attendance and active participation in diabetes school classes is an important element in disease management. It has been noted that self–learning and self–help predetermine the clinical outcomes of diabetes and the quality of life of patients.

Aim

To evaluate the awareness of patients with type 2 diabetes (T2D) about their disease.

Materials and methods

45 patients with T2D were included. The survey contained 5 questions: A questionnaire based on the Diabetes Care Profile (DCP) questionnaire was offered to all participants. As part of this work, the following sections have been analyzed: school diabetes, glucose self-control (which includes questions on hypo-and hyperglycemia), power supply, physical activity, prosperity, complication control, observance of the recommendations for treatment of the disease.

Results

55.5% (25) are willing to watch, observe, and only one in five (20.0% (9)) would like to communicate interactively. One in three patients with type 2 S.D. does not self–monitor glucose until 33.3% in the morning and 35.6% two hours after a meal. The presence of symptoms of hypoglycemia was indicated by patients who received either insulin treatment or insulin treatment in combination with oral drugs (44.4%). 43.2% experience hyperglycemia and 54.5% do not. 28.2% do not take any action on this issue, and 33.3% increase their short insulin dose. Only 10.3% increase the dose of prandial insulin or resort to physical activity. 12.8% and 15.4% either consume more fluid or skip staple foods or snacks, respectively. 55.8% exercise regularly. And 44.3% do not pay due attention to this recommendation.70.1% noted that their physical activity is light, 27.0% have a moderate load. 46.0% do not agree that they are healthy. 35.1% find it difficult to answer the question unambiguously and 18.9% feel healthy. According to 55.3% of patients, diabetes interferes with other aspects of life, 26.3% do not know how to answer the question, and 18.4% disagree. 41.0% of patients experience high levels of stress and one in four 25.6% are unfamiliar with these feelings by self-esteem.

Conclusion

Patients with type 2 DM are familiar with the main actions in hyperglycemia, but the practical application of these recommendations does not give proper results. Half of those interviewed do not feel healthy and the disease interferes with other aspects of their lives. Many agree that they are making efforts to control the disease, but are not aware of what this concept includes.

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EP141

Frequency of hyperglycemia in screening of pregnant bulgarian women

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Bulgaria is also among the countries with national data on the prevalence of Diabetes published in the Diabetes Atlas of the International Diabetes Federation'2019, but did not provide data on the incidence of Hyperglycemia in pregnant Bulgarian women.
Purpose
The Bulgarian Society of Endocrinology organized and conducted screening for Hyperglycemia in pregnant women in 2019.
Material and methods
547 pregnant women from 10 regions of Bulgaria (84 settlements) were examined, with an average age of 30±5 y, an average BMI at screening 26.15±7.28 kg/m2, distributed by trimesters – I (*n* – 111, 20.3%), II (*n* – 275, 50.4%), III (*n* – 161, 29.3%). The diagnostic criteria for hyperglycemia in pregnant women were in compliance with FIGO'2015 / WHO'2013 and NICE'2015.
Results
Hyperglycemia was detected in 74 (13.52%) of the pregnant women according to oGTT screening data, with 5.66% (*n* – 31) diagnosed with early pregnancy and 7.86% (*n* – 43) – Gestational Diabetes Mellitus (GDM). There is no evidence of pre–pregnancy hyperglycemia or antidiabetic medication. Family burden with Diabetes was found in 210 pregnant women (38.4%). This family burden is present in 58.1% of all pregnant women with hyperglycemia (*n* – 43/74) – in 67.7% of pregnant women with early hyperglycemia (*n* – 21/31) and in 51.2% of pregnant women with GDM (*n* – 22/43). It appears that the risk of hyperglycemia is twice as high in the presence of familial diabetes with 20.4% (*n* – 43/210) compared to the lack of familial diabetes with 9.2% (*n* – 31/337). The average weight before pregnancy of the whole group is 63.68±14.36 kg, and during pregnancy it reaches 70.60±14.50 kg. The average weight before pregnancy is 71.00±16.30 kg of pregnant women with established hyperglycemia during pregnancy, which plays an important role in unlocking glucose intolerance.
Conclusion
The high incdence of hyperglycemia in pregnant Bulgarian women requires changes in the health system to diagnose this disorder in a timely manner.

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EP142

The impact of fasting during ramadan on the sleep 9 wake rhythm in type 2 diabetics

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Introduction
Fasting during Ramadan is a pillar of Islam. The majority of diabetic patients at risk, practice it even if they are exempt. This practice shifts energy and hydration in the evening and reverses the sleep–wake rhythm. The aim of this work is to study the effect of fasting during the holy month on the sleep–wake clock in fasting diabetics.
Patients and methods
As part of an overall management of accompagnimant for our diabetic patients, an integral health action that aims to stratify the risk for fasting, was carried out before Ramadan in 2019. A questionnaire on sleep habits was completed one week before Ramadan and one month after. Two scales of drowsiness and tiredness were also completed.
Outcomes
Among the 176 participants in this company, 81 type 2 fasting diabetics were collected to answer the sleep quality questionnaire. The total reported sleep duration was much shorter during Ramadan. Fatigability and daytime sleepiness were present in 68% of patients during Ramadan, vs 28% after this month with no notable incidents. The duration of the revealed daily nap was much longer during the holy month with an average of 150 minutes, compared to 90 minutes outside of Ramadan.
Discussion/Conclusion
The effect of fasting during Ramadan on sleep patterns, daytime sleepiness is an interesting topic that provides a highly complex context for future research.
Our observational and analytical study shows that fasting during Ramadan leads to insufficient night sleep with a non–compensatory increase in the duration of daytime naps.
These changes could be related to lifestyle changes that accompany Ramadan fasting rather than the act of fasting itself. Larger studies that control for different confounding factors, such as environmental and cultural factors, are needed to assess the impact of Ramadan fasting on sleepiness. In addition, it is important to assess the impact of Ramadan fasting in different Islamic cultures using the same assessment methods.

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EP143

Lipoatrophy in a patient with type 1 diabetes: Genetic or immunological?

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We report the case of a 28-year-old Emirati lady with type 1 diabetes (weight 51 kg, BMI 20.82 kg/m^2) diagnosed at 3 years of age who presented to our centre with problems at her insulin injection sites. She had poor glycaemic control and her diabetes was complicated by retinopathy; other past medical history included vitamin D deficiency. All her seven siblings had diabetes and were on insulin; both parents had type 2 diabetes.
In 2017, she was switched from insulin glargine to insulin degludec and 7 months later she developed pronounced lipoatrophy (both upper frontal aspects of thigh) at the injection sites. She also developed hyperpigmented and hypertrophic reticular lesions on both axillae and neck, which were histologically proven acanthosis nigricans. She was treated with minocycline and this resulted in some improvement.
Further investigations included serum leptin and C3 nephritic factor, which were within normal range. Genetic testing showed a heterozygous variant in the Lipase E (LIPE) gene [c.746C>T p. (Thr249Met)] that was reportedly of uncertain significance. LIPE gene encodes hormone–sensitive lipase (HSL) that hydrolyzes triglycerides in adipose tissue. Mutations in this gene are associated with familial partial lipodystrophy. Attempted adipose tissue transplant was unsuccessful as transplanted tissue also atrophied within 2 weeks.
The lipoatrophy in this patient was severe and continued in spite of avoidance of injections at the lesions. It is likely that immunological factors are important in its aetiology. The heterozygous variant in LIPE gene is very rare and has not been previously described in the Emirati population. The strong family history suggests genetic cause for this patient's diabetes, which may also be relevant in the aetiology of her lipodystrophy. In the reported case here, there were also major psychological and cosmetic sequelae which contributed to her poor glycaemic control which have proved challenging to treat.

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Cardiovascular diseases in people with diabetes mellitus in asturias from 2013 to 2017

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Aim
Atherosclerotic cardiovascular disease, defined as myocardial infarction (MI), cerebrovascular accident (CVA), peripheral artery disease (PAD), is the main cause of morbidity and mortality in people with diabetes mellitus (DM) and the main cause of health expenditure in these patients.
Like in other parts of the world, a prospective study of the Asturian population showed that the mortality risk due to cardiovascular diseases was significantly higher in women with DM2 than in men.
The aim of this study is to compare the odds ratio of cardiovascular disease in people diagnosed of DM with those not diagnosed of DM based on age and sex, in the Asturian region between 2013 and 2017.
Materials and methods
Data were collected from the Primary Healthcare Clinical Database of the National Health System for the Principality of Asturias, between 2013 and 2017. The people with DM and non–DM were grouped by sex and age (35 to 64 and people over 64 years). In addition, the comorbidities both diagnosed and non–diagnosed were recorded as follows: MI, CVA and PAD.
Odds ratio, confidence intervals (95%) were calculated in R environment. Graphics were performed in GraphPad Prism 8.0.1.
Results
In all the years (2013 to 2017) it was observed that people with DM, regardless of age and sex, were more likely to suffer from any of the three cardiovascular diseases.
When analysing the data stratified by age, people with diabetes between 35 and 64 years are more likely to suffer from MI, CVA or PDA; a progressive decrease in ORs can be perceived from 2013 to 2017, in patients with DM in ages between 35 and 64 suffering from PAD (4.35 [4.06 – 4.66] and 3.09 [2.88 – 3.31] respectively).
When the data is separated by sex, the youngest age group is at greater risk of suffering from any cardiovascular disease. Diabetic women between 35 and 64 years of age were more likely than men to suffer from MI, while the opposite was appreciated for CVA and PDA. Likewise, a tendency to increase the odds from 2013 to 2017 was observed in this group.
Conclusions
Comprehensive and aggressive control of known risk factors for cardiovascular disease is needed in diabetic patients, especially those younger and females, in order to reduce the high prevalence of cardiovascular complications seen in Asturias.

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Association between change of lipid profiles and early postpartum hyperglycemia risk in chinese women with prior gestational diabetes mellitus

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Aims
Maternal dyslipidemia during pregnancy is more serve in GDM women compared with non–GDM women. The occurrence of postpartum hyperglycemia is associated with increased lipid profiles. The purpose of this study was to evaluate the relationship between lipid changes and early postpartum abnormal glucose metabolism (AGM) of women with prior GDM history.
Methods
395 patients with a history of GDM who had a postpartum OGTT were included in this retrospective cohort study. Patients' lipid levels at the gestational 2nd, 3rd trimester and early postpartum, which included total cholesterol (TC), triglycerides (TG), low–density lipoprotein cholesterol (LDL–C), high–density lipoprotein cholesterol (HDL–C) and TG/HDL–C ratio were recorded. HOMA–IR was used to evaluate insulin resistance and ISSI–2 was applied to assess pancreatic β cell functions. Logistic regression and Spearman correlation analysis were applied to determine the relationship between postpartum lipid change and glucose metabolism.
Result
Postpartum AGM patients ($n=153$) were with higher postpartum triglycerides (TG) and TG/HDL levels than women with normal glucose tolerance (NGT) ($n=242$). TG, TC, LDL–C, concentration and TG/ HDL–C ratio increased gradually during pregnancy and decreased after delivery, while HDL–C levels constantly decreased from 2nd trimester to early postpartum, the trends were similar in the postpartum AGM group and NGT group. Logistic regression analysis showed that decrease ratio of TG after delivery was associated with a decreased risk of early postpartum AGM. Correlation analysis indicated that ratio of TC, TG, LDL–C and TG/HDL–C were associated with the restoring of insulin sensitivity and pancreatic β cell function.
Conclusion
Postpartum changes in blood lipid level in GDM patients are closely related to hyperglycemia in the early postpartum, and effect of the decrease of TG was the most significant. The specific mode of action may be related to insulin resistance and pancreatic β cell function.

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EP146

Uricemia and renal function in type 2 diabetics

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Introduction:
Due to the association of hyperuricemia with conventional cardiovascular risk factors, it is difficult to determine whether uric acid is an independent risk factor for the development of renal failure. The objective of this study was to investigate the correlation between uric acid levels and kidney function in type 2 diabetics.
Methods
This was a descriptive cross–sectional study carried out from March to September 2017 on 122 diabetic patients hospitalized at the National Institute of Nutrition. Each patient underwent a clinical examination with a standard assessment including the determination of creatinine and uric acid. Creatinine clearance was calculated using the CKD–EPI formula.
Results
The average age of our patients was 52.4±7.3 years. The sex ratio was 0.96. All patients in our population were type 2 diabetics and the average duration of diabetes was 11.07±3.3 years of which 78.7% were on insulin therapy. The patients in our study were smoking at 35.2%, sedentary at 39.8%, hypertensive at 45.1% and presented with biology a hyper-LDLemia at 56.2%. Uricemia was positively correlated with creatinine level ($P=0.41$; $P<0.05$) and inversely correlated with creatinine clearance. The level of uric acid varied according to the stage of the renal insufficiency; indeed it increased if the renal function was deteriorated ($P<0.005$). Uricemia is also positively and statistically correlated with the number of cardiovascular risk factors in type 2 diabetics ($P<0.05$).
Conclusion
Our work has shown that uric acid levels are correlated with kidney function which could be an aggravating factor for this impairment. However, our population was small and not representative of the population, hence the need for large–scale studies.

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EP147

Ramadan fasting affects body composition and anthropometric parameters in type 2 diabetic patients.

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Introduction
Fasting the month of Ramadan is practiced by more than one billion Muslims worldwide, including type 2 diabetic patients. Its effects on body composition and body weight in type 2 diabetic patients are controversial.
The objective of our study was to assess the evolution of anthropometric parameters as well as the body composition in type 2 diabetic patients who fasted the month of Ramadan.
Methods
We conducted a prospective case–crossover study including 55 type 2 diabetic patients treated with metformin and / or sulphonylurea, with an HbA1c <10% and who intended to fast the month of Ramadan 2019, in the absence of a major contraindications. Body composition and anthropometric parameters (body weight, body mass index (BMI) and waist circumference (WC)) were evaluated in three sessions: T0: before the month of Ramadan, T1: just after the month of Ramadan and T2: 1 to 2 months after Ramadan month.
Results
Participants had an average age of 54.5±10.1 years and a sex–ratio of 0.89. The average HbA1c before the month of Ramadan was 7.13±0.95%.

Eighty–nine percent of patients fasted 30 days. There was a significant body weight loss after Ramadan fasting ($p<10^{-3}$). The BMI was 29.51±5.13 kg/m^2 before Ramadan, 29.22±5.42 kg/m^2 at T1 ($P=0.004$) and 29.56±5.01 kg/m^2 at T2 ($P=0.05$). The WC clearly decreased at T1 (T0=97.6±8.92 cm vs T1: 96.37±10.22 cm; $P=0.015$) but not at T2 (WC=97.13±8.03, $P=0.55$). Compared to T0, there was a decrease in the fat mass at T1 (T0=23.69±9.32% vs T1=23.28±9.5%, $P=0.043$) but not at T2 (T2=23.77±9.26%, $P=0.24$). The fat mass index varied from 8.92±3.92 at T0 to 8.82±4.12 at T1 ($P=0.04$) and to 8.93±3.76 at T2 ($P=0.24$). Body weight loss at T1 was positively correlated with the number of fasted days ($r=0.348$, $P=0.018$). However, it was not correlated with dietary intake variations and the physical activity.
Conclusion
Ramadan fasting had a favorable and a significant effect on the body composition, the body weight and the WC in type 2 diabetic patients. However, this improvement was not sustainable one month later.

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EP148

Study on glutamic acid decarboxylase antibodies (Anti–GAD) in blood serum for early diagnosis of diabetes mellitus

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There are three main types of diabetes mellitus: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) and gestational diabetes, with the first two types making about 99% of cases.
According to its nature, type 1 diabetes mellitus (T1DM) is considered as a typical autoimmune disorder characterized with specific autoantibodies. Immunological markers of the diabetes mellitus onset can be found not only in T1DM with its specific clinical picture, but also in T2DM. Glutamic acid decarboxylase antibodies (Anti–GAD) are a DM immunological marker both of clinical and academic interest.
The work was initiated to study predictive value of specific glutamic acid decarboxylase antibodies as the immunological marker.
Anti–GAD concentrations were measured in the blood serum of a proband, a patient with type 1 diabetes mellitus. The enzyme–linked immunosorbent assay with the ELISA kit for Anti–Glutamic Acid Decarboxylase Antibody (Anti–GAD) (Cloud–Clone Corp., Houston, USA) was used for Anti–GAD qualitative determination in plasma and blood serum of the patients. Variation statistics was used for statistical processing of the results.
Anti–GAD concentrations in the probands' blood were found to be 1.54 times higher than those in blood of the apparently healthy controls ($P_1<0.0001$). The similar picture could be seen after examination of a proband's family members with Anti–GAD concentrations 1.9 times higher than those in the controls. Among other things, this seemed to be associated with the presence of the diabetics among the probands' family members. It can be explained by the genetic predisposition to DM onset and progression in some family members as well.
Identification of Anti–GAD in patients with the diagnosed DM, as well as in some of their close relatives can serve as a confirmation of predictive value of the immunological marker.

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EP149

Vitamin D deficiency in children and adolescents with type 1 diabetes mellitus

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Introduction
Besides its role in calcium homeostasis, vitamin D (VD) has an important immune mudulation effect. However, its role in autoimmune diseases such as type 1 diabetes is under discussion. In this study, we aimed to assess VD status in children and adolescents with type 1 diabetes mellitus (T1DM).
Material and methods
This is a retrospective descriptive study realized at the endocrinology–diabetology department of OUJDA's Mohammed VI university hospital, included 120 type 1 diabetics under the age of 19 years, with evaluation of vitamin D status.
Results
The sex ratio in our study was 1.2 (M/F) with a mean age of 13.4±4.15 years. 32.2% have a history of type 1 diabetes mellitus over 5 years. The mean HbA1c was10.97±2.42 %.
Of 120 of cases with T1DM, most had inadequate levels of vitamin D: sufficiency, 3.3% ($n=4$); insufficiency, 75 % ($n=90$); deficiency, 21.7% ($n=26$). In bivariante analyses for age, sex, visit season, z–BMI, diabetes duration, and A1c, age was most significantly associated with the level of 25OHD ($P<0.037$, r –, 191*); older age was associated with lower 25OHD concentrations.
Discussion and conclusion
Previous studies have shown that the early years of adolescence are often associated with a rapid decline in vitamin D.
Because of many risk factors that may not be modifiable due to the inherent presence of diabetes mellitus, vitamin D deficiency during childhood and during the period of peak bone mineral accumulation in this population is justified.

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EP150

Effect of socioeconomic and educational status on metabolic control in patients with diabetes mellitus type 2 in republic of srpska

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Aim
To determine the effect of socioeconomic and educational status on metabolic control in T2D patients in Republic of Srpska (RS)
Subjects and method
This is a cross–sectional study of 1088 subjects aged 18 or higher who were randomized from primary care physicians' T2D diabetes registries. Socioeconomic, educational, anthropometric and metabolic characteristics of T2D patients were analyzed.
Results
Highest proportion of participants were older than 65 (47.9%) with 55% women and 44.5% men. 65.3% were retirees with single monthly income (61.4%) of up to 300€ (63.2%). More than half of participants had elementary level or no education at all. Unsatisfactory HbA1c level was statistically significantly more common (61.1%:38.9%, $\chi^2=4.874$, df=1, $P=0.027$) in patients of low socioeconomic and educational status. Half of participants were obese (BMI≥30kg/m^2) and 75% had abdominal obesity with elevated levels of cholesterol (75.6%), LDL (86.0%) and triglycerides (54.3%), and low HDL levels (55.9%). Albuminuria and proteinuria were reported in 59.7% and hypertension in 88.61% of subjects.
Conclusion
High percentage of T2D patients of low socioeconomic and educational status in Republic of Srpska has not achieved target values of good metabolic control, is obese and has microalbuminuria. This could be related to low educational level, low monthly income and older age. Since most participants live with other family members it is necessary to educate those family members to take active part in realization of health guidelines for diabetes management.

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EP151

Incidence of chronic diabetes complications and its association with glucoregulation quality and antihyperglycemic treatment in patients with diabetes mellitus in republic of srpska

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Aim
Chronic diabetes complications are the main cause of patients' mortality, life span shortening and decreased quality of life. Aim of this study is to determine the incidence of chronic diabetic complications and their association with glucoregulation quality and antihyperglycemic treatment in diabetic patients in Republic of Srpska. (RS).
Method
This cross–sectional study included 1037 diabetic patients in RS. Immuno–inhibition test (Roche Diagnostics) was used for measurement of HbA1c. Anthropometric and blood pressure measurements, screening for chronic complications of diabetes and antihyperglycemic treatment questionnaire were included.
Results
Poor glycemic control (Hba1c ≥6.5%) was found in 61.1% of subjects (χ^2=4.874, df=1, P=0.027). The most common complication was microalbuminuria –nephropathy (48.10%), followed by polyneuropathy (42.5%) and retinopathy (25.0%). Polyneuropathy and microalbuminuria were more common in T2D (χ^2=10.217, df=1, P=0.001), while retinopathy was more common in T1D. Cardiovascular disease was recorded in 81.4%, significantly more often in women (87.0 vs 75.9%) than men (χ^2=21429, df=1, P=0.000). Significantly more men (5.5%) than women (2.3%) had diabetic foot (χ^2=7.237, df=1, P=0.007). In patients with T1D on diet and insulin treatment microvascular complications and hypertension were less common compared to patients on insulin only. In T2D the same is found with combination treatment (insulin plus diet and/or oral therapy) compared to oral only treatment.
Conclusion
High percentage of diabetic patients in RS have poor glucoregulation, hypertension, nephropathy and cardiovascular disease . Many studies from developing countries have shown similar results thus underlying the need for implementation of stronger measures for improving glucoregulation and reducing chronic complications.

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EP152

Laser doppler flowmetry and fluorescence spectroscopy in assessing the state of the microvasculature and oxidative metabolism in patients with diabetes mellitus

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Purpose
To study the state of the microvasculature and tissue metabolism (according to the dynamics of the FAD and NADH coenzymes) using laser Doppler fluometry (LDF) and laser fluorescence spectroscopy (LFS) in patients with diabetes mellitus.
Materials and methods
To implement the combined use of LDF and LFS methods, the Laser Diagnostic Device LAZMA ST was used (registration certificate of Roszdravnadzor No. RZN 2017/5844 of June 08, 2017).
The study was conducted on the sole of the big toe, with pre–treatment with an alcohol solution of the surface of the toe.
Criteria for non–inclusion: the presence of violations of the main bloodstream of the vessels of the lower extremities.
Control group: 30 people. Non–inclusion criteria: the presence of cancer, changes in the main blood flow of the lower extremities.
In patients, glycated hemoglobin (HbA1c) was assessed.
Results
40 patients with diabetes mellitus aged 30 to 70 years were examined using LDF and LPS using functional tests (local thermal and cold tests): 29 women and 11 men. Of these: type 1 diabetes in 3 people, type 2 diabetes in 37 people.
Patients were divided into the following groups:
1) Subcompensated violations:
1 1a – active microcirculation, oxidative metabolism reduced: 14.
2b – microcirculation is inactive, oxidative metabolism is reduced: 4.
3c – active microcirculation, oxidative metabolism reduced markedly: 9.
2) Moderate decompensated disorders of microcirculation and oxidative metabolism: 11.
3) Severe decompensated disorders of microcirculation and oxidative metabolism: 2.
Conclusions (conclusion)
A direct correlation was revealed between the HbA1c indices and the degree of microcirculatory disorders and oxidative metabolism: in group No. 1, HbA1c ranged from 6.5% to 7.2%; in group No. 2 HbA1c in the range of 7.5% – 10.2%; in group No. 3 HbA1c in the range of 10.7% – 12.1%.

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EP153

Effect of hypoglycemic therapy with forsiga on indicators of carbonyl (methylglyocal) and oxidative stress (MDA) in patients with NAFLD and type 2 diabetes

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Methylglyoxal (MG) damages arginine protein residues, inhibits enzymes, disrupts insulin signal transmission, and plays a key role in the development of insulin resistance and hyperglycemia. High glucose levels cause an increase in glycation and methylglyoxal formation. Glycation is the main cause of protein damage, leading to the production of free radicals and causing inflammation.
The purpose of the study
To Identify the relationship of methylglyoxal content with markers of inflammation (retinol–binding protein). The lipid peroxidation level was determined by the content of malondialdehyde (MDA). Determine the level of MG content by high–performance liquid chromatography.
Materials and methods
208 patients with NAFLD and type 2 diabetes were examined. There were 76 patients with type 2 diabetes and 132 with impaired glucose tolerance (NTG). The average age is 57.3±5.2 years. BMI34, 85±1.79. In 30 patients conducted hypoglycemic therapy with a medication Formiga (of dapagliflozin).
Research results
In 30 patients with NAFLD and DM, the serum MG content of 520.75±114.35 nm/l was 283.3±11.5 nm/l, in the control group of 251.3±53.6 nm/l.
Retinol–binding protein as a marker of type I and type 2 diabetes in this group of patients was increased and amounted to 55.83±2.92 mg/l compared to the control group of 26.15±1.31 mg/l (P=0.001). Hyperglycemia increases the processes of lipid peroxidation. MG and MDA are correlated (r=0.495).
Conclusions
Glucose–lowering therapy with a medication Forsiga leads to a decrease in the level of hyperglycemia, the level of MG and processes of lipid peroxidation.
MDA up to 24.12+1.64 mmol/l p/l 16.9+3.86.
MGL 192.11+16.34 nm/l

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Hereditary pancreatitis as a rare cause of diabetes mellitus in the youth

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Introduction
Most cases of Diabetes mellitus (DM) in children and adolescents are autoimmune (type 1), even though recently there has been an increase in type 2 DM mainly due to the increased prevalence of obesity in this age group. However, rarely DM could be attributed to other causes such as MODY. An extremely rare cause is the hereditary pancreatitis due to activating mutations of the PRSS1 gene. This gene encodes an enzyme, cationic trypsinogen, whose hyperactivity leads to prolonged intrapancreatic effect of trypsin. This destructive process of pancreatic tissue results in diabetes, recurrent pancreatitis and pancreatic cancer. .
Case Presentation
A 16–year old male adolescent presented to our department with typical diabetic symptomatology. He was in good general condition without ketoacidosis. Fasting glucose was 266 mg/dL and HbA1c 10.9%. The antibodies for type 1 DM were negative with the exempt of those against the zinc transporter ZnT8. C–peptide was measurable although inappropriately low for his high blood glucose. Despite the high HbA1c, the patient was treated with metformin and lifestyle modification resulting in excellent metabolic control (fasting blood glucose 80–120 and 2 hours postprandially < 140 mg/dl). Further genetic investigation for MODY, especially MODY3 which is the most common form, was negative. Subsequent screening for other types of DM revealed an activating mutation of the PRSS1 gene.
Conclusion
When the diagnosis of type 1 diabetes mellitus in children and adolescents cannot be established with safety and genetic testing for MODY is negative, screening for PRSS1 gene mutations must be performed. If the result is positive, additional counseling should be pursued regarding the nature and progression of this hereditary disease as well as the future possibility of pancreatic cancer.

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EP155

Two types diabetes mellitus: clinical case of HNF1B–mody and type 1 diabetes in one patient

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Hyperglycemia in a 27–year–old woman without obesity was found in the first trimester of her third pregnancy in 2015 (fasting plasma glucose – 5.8 mmol /l). Gestational diabetes was established and insulin was initiated in basal–bolus regimen. After delivery the blood glucose was normal due two months then hyperglycemia increased to 15 mmol/l. Metformin and glimepiride were prescribed within effect. Then insulin detemir (8 U/day) was prescribed with DPP–4 inhibitor sitagliptin and SGLT2 inhibitor empagliflozin. In 2016 analysis for all antibodies were negative, the fasting C–peptide was 553 pmol/l (normal: 298–2350 pmol / l) and 1129 – postprandial. Molecular genetic testing was done in 2017. Mutation in the *HNF1B* gene (rs138986885) (MODY5) was diagnosed. In addition it was found that the patient is carrier of heterozygous variant rs2476601 in the tyrosine phosphatase gene (PTPN22) which is associated with an increased risk of developing type 1 diabetes mellitus (T1DM). No other clinical phenotypes associated with mutations in *HNF1B* were found. No other cases of diabetes in relatives have been reported. The same mutation in the HNF1B gene was found in mother and daughter of a proband with normal level of glucose when examining family members. In 2018 blood glucose level was 16 mmol/l, concentration of C–peptide decreased to 83 pmol/l. Tableted therapy was canceled and baseline bolus insulin therapy was started. In 2019 HbA1c level was 7.13%. Further decrease in pancreatic cell function was noted: fasting C–peptide 33.3 pmol/l, after eating 91.9 pmol/l. The patient was transfer to pump insulin therapy. Clinical case shows a rare combination of two types of diabetes mellitus with progressive, aggressive course of disease.

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EP156

What should be the cut–off age for active screening for type 2 diabetes in Uzbekistan?

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Background
Different screening programs recommend starting active search for type 2 diabetes (DM2) at age from 35 to 45. This difference comes from variety in structure of population and weight of age as a risk factor, and also has economical background.
The aim of our study
Was to find out the most acceptable cut–off age for DM2 screening in Uzbekistan.
Material and methods
We analyzed results of type 2 diabetes screening in three regions of the Republic of Uzbekistan among 2521 people aged 35 or older without known carbohydrates metabolism disorders. A1c was tested using method of immune precipitation with anti–human and anti–mouse A1c antibodies (Human), oral glucose tolerance test was performed with 75 g glucose. Diabetes was diagnosed according to IDF recommendations.
Results and discussion
In total, DM2 had 7.9% of analyzed population. When comparing the age groups, DM2 was revealed in 0.92% (1.1% in men and 0.9% in women) at age 35–39, in 3.4% (5.1% in men and 2.9% in women) at age 40–44, and 11.8% (12.1% in men and 11.6% in women) at age 45 or older (10.5% at age 45–59; 16.5% at age 60–74; 11.9% at age 75 or older, which is 11.4%, 16.0%, and 5.6% in men, and 9.9%, 16.7%, and 14.2% in women, respectively). So, significant rise in diabetes was revealed starting from age 45.
Conclusion
Taking into account economic issues, we recommend to start screening for type 2 diabetes in Uzbek population at age 45.

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EP157

Lodine saturation in Czech patients with type 1 diabetes mellitus

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Background of the study
There is lack of data in the Czech Republic on iodine status in patients suffering from diabetes mellitus type 1 (DM1) considered to be at risk of iodine deficiency.
Subjects and methods
A total of 54 males and 51 females Cmedian (25th, 75th percentile): age (years) 42 (31, 55); BMI 25.9 (23.3, 29.7); HbA1c (mmol/mol) 61 (51.2, 71.0) treated for DM1 were included in this cross–sectional study. In addition to iodine saturation determined as the concentration of iodine in the first urine sample of the day, we measured clinical, anthropometric, and biochemical parameters related to DM1.
Aims of the study
The main aims were to obtain for the first time information about iodine saturation in Czech patients with DM1; and to determine a) to what extent this saturation differs from the non–diabetic population, b) whether iodine saturation is related to selected clinical and laboratory parameters and characteristics of diabetic syndrome.
Results
Measured iodine levels were: median 152 μg/l, 25th percentile 117 μg/l, and 75th percentile 219 μg/l. More than 50% of iodine levels were within the optimal saturation range of 100–200 μg/l, while about 14% showed incomplete saturation (<100 μg/l), and 34% had increased saturation (>200 μg/l). Multi–dimensional regression showed significant positive relationships ($P < 0.01$; an OPLS model explaining 9% of the variability) between ioduria and male sex, body weight and height, and serum creatinine levels, which to

date have not yet been published in DM1 patients. Relationships to the other analyzed parameters (HbA1c, insulin dose, DM duration, body mass index, microalbuminuria, glomerular filtration rate, thyroid function and volume, thyroid autoimmune markers) were not significant.
Conclusions
We found that Iodine saturation in our DM1 patients were within the IC-CIDD (WHO) recommendations for optimal/good saturation for the non–diabetic population. We believe that long–term efforts to deal with iodine deficit in the general population of the Czech Republic are responsible for the satisfactory iodine status of the DM1 patients as well.
We did not find any significant relationships between iodine saturation and characteristics of diabetic syndrome, but multi–dimensional regression analysis found a new, as yet. unpublished positive relationship between ioduria and male sex, body weight and height, and creatinine levels.
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EP158

Correlation between pro–inflammatory biomarkers and vitamin B12 levels in diabetes mellitus: A prospective study

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Introduction
Apart from genetics, autoimmunity has been implicated in pathogenesis of diabetes mellitus (DM). Further the role of vitamin B12 levels in diabetic immunomodulation is controversial. In this context, we set out study the role of Pro– inflammatory cytokines in DM with or without vitamin B 12 deficiency in South Indian population.
Material and methods
This prospective case–control study was conducted on diabetes mellitus patients. Institutional ethical committee approval was obtained. Exclusion criteria were subjects with any systemic or chronic inflammatory disease or taking B12 supplements, proton pump inhibitors or any medication which interferes with the normal function of the hypothalamic–pituitary–gonadal axis. Serum samples were collected from 100 diabetic subjects and 20 age matched healthy controls. Cases were divided in to two groups A and B with deficient and sufficient serum vitamin B12 levels respectively. Controls are considered as group C. Interleukin–6 (IL–6), Tumour necrosis factor–alpha (TNF– α) and high sensitive C reactive protein (hsCRP), leptin levels were measured in all serum samples. Statistical analysis was performed by one way ANOVA with Dunnet's test and Pearson correlation tests.
Results
The mean hSCRP level in groups A, B and C were 17.1 ± 3.1 mg/ml, 6.3 ± 0.9 mg/ml and 5.6 ± 1.2 mg/ml respectively. The mean TNF– α, IL–6, Leptin levels in groups A and B were 278 ± 32 pg/ml, 12.8 ± 4.3 pg/ml, 2.85 ± 0.8 ng/ml and 168 ± 21 pg/ml, 4.8 ± 1.3 pg/ml, 11.85 ± 2.7 ng/ml respectively. The corresponding values in group C were 147 ± 16 pg/ml, 3.8 ± 1.1 pg/ml, 10.66 ± 1.7 ng/ml. There was statistically significant difference of all the pro–inflammatory cytokines compared between group A with B and C (P value < 0.05) with negative correlation for leptin levels. Similar comparision between group B and control group C was not statistically significant (P value > 0.05)
Conclusions
Our study showed diabetic patients with raised titers of pro–inflammatory markers – IL–6, TNF–α and hsCRP, while reduced leptin levels correlated significantly with vitamin B 12 status, suggesting its significant contributory role. But, the exact immuno–modulatory role and pathogenetic mechanism of vitamin B12 metabolism needs more research.
Keywords: diabetes, tumour necrosis factor, interleukin–6, goiter, auto–immunity, leptin.
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Serum 25-oh vitamine d level in patient with Psoriasis in Korca, Albania- A case-control study

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Background
Psoriasis is a common chronic, inflammatory skin disease that may exhibit a variety of clinical manifestations. Psoriasis has also been identified as a multisystem chronic inflammatory disorder associated with multiple comorbidities. Recently has been reported a role for vitamin D in the pathogenesis of different skin diseases, including psoriasis.
Aim
The objective of this study was to measure the serum level of vitamin D in patients with psoriasis and compare it with the level in the control group.
Materials and Methods
The study was conducted in the department of dermatology.100 cases were included, 50 patients clinically diagnosed with psoriasis and 50 normal people. The level of Vit D was measured with k–imunofluoresence. Normal level > 30 ng/ml = vit D sufficiency, levels 11–30 ng/ml = vit D insufficiency, levels <10 ng/ml = vit D deficiency. The testing of vitamin D was done during the fall. The characteristics of the population in the study. Psoriatic patients:60% of the patients were male and 40% were female.10% of women were black skin.10 % of men were black skin.15% of women were in menopause. The average age was 44.1 years ± 17 SD (min = 11, max = 78 years old).In the control group the selection for this people is casual. These patients may or may not suffer from any other disease. 20% of them were male and 80% were females. The average age 38.54 years old ± 16.53SD (min = 1, max = 72 years old).
Results
In the psoriatic patients group the average value of vit D was 16.623 ± 6.35 SD, (min = 6.08 ng/ml, max = 37.4 ng/ml).4 patients or 8% had a Vit D level between 0–10 ng/ml, 29 patients or 58% had a Vit D level between 11–20 ng/ml, 15 patients or 30% had a Vit D level between 21–30 ng/ml. Only 2 patients or 4% had a normal Vit D level >30 ng/ml. There is no difference of the average value of vit. D between males and females in this group. In the control group the average value of vit D was 19.8 ± 6.86 SD(min = 5.61 ng/ml, max = 35 ng/ml). 4 patients or 8% had a Vit D level between 0–10ng/ml, 21 patients or 42% had a Vit D level between 11–20 ng/ml, 22 patients or 44% had a VitD level between 21–30 ng/ml. Only 2 patients or 6% had a normal Vit D level >30 ng/ml. There was a higher value of vit D in males without psoriasis, compared to women.
Conclusion
There was reduced vitamin D level in psoriatic patients when compared to healthy controls. The number of people with vit D deficiency and sufficiency was equal in both groups. The number of people with vit D insufficiency was higher in the psoriatic group.
Keywords: 25–OH Vitamine D, serume level, Psoriasis.
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EP160

The characteristics of carbohydrate metabolism during cushing's disease

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Introduction
Cushing's disease is diabetogenic due to the insulin resistance generated by the stimulating effect of glucocorticoids on neoglucogenesis and hepatic glycogenolysis.
Goal
Aim of our work is to study the frequency and characteristics of diabetes mellitus during Cushing's disease.
Material and methods
Retrospective study of a sample of 100 patients collected between (January 1983 – December 2009) in the endocrinology department of the CPMC.
Results
The frequency of diabetes mellitus in our series is 58.5%, (n = 58 p), the average age is 40 years, with a sex ratio of 3/1 (3F, 1H), diabetic inheritance is present in 75% of cases, the average BMI of our diabetic patients is 29.5 kg / m 2, the average CLU is 826 mg / 24 h, hypertension and dyslipidemia represent 80% and 52% respectively. Half of our patients (n = 29) are treated with insulin therapy (insulin alone n = 19, mixed treatment: insulin + oral treatment n = 10). The good glycemic balance under treatment was obtained in 30% (n = 17p), the average glycemic for all our diabetics is 2.33 g / l

for fasting glycemia, extremes (1.4– 3.6), and 2.56 g / l for post prandial, extremes (1.7 – 4.2).
Conclusion
The high prevalence of diabetes mellitus during cushing's disease requires rigorous monitoring with early detection of the other atherogenic risk factors which are often associated in order to improve management and to prevent complications, especially cardiovascular, which can initiate vital prognosis.

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EP161

To estimate the prevalence of obesity and abdominal obesity in adult patients

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Background and aims
Obese people have more risk for hypertension, Diabetes mellitus and cardiovascular disease. Obesity is a major health issue globally. So our aim is to estimate the prevalence of obesity and abdominal obesity in adult patients.
Materials and methods
In our study total 150 adults (> 20 years of age) patients were included. They were selected randomly & examined for BMI (body mass index) and WHR (waist to hip ratio).
Results
In this study out of 150 patients males were 92 and females were 58. WHR ranged in males 0.69 to 1.34 and in females 0.66 to 1.41. As per WHR, males (1.08±0.06) were more obese than their female (0.99±0.08); $P<0.001$. BMI ranged in males 16.78 to 45.34 kg/m^2 and in females 18.74 to 52.73 kg/m^2. BMI in females (29.52±5.25) was comparatively more than males (25.78±3.46); $P<0.001$. According to BMI, the overall obesity prevalence in our study population was 22.8%; obesity prevalence in males was 14.68% and in females 36.42%. The overweight prevalence was 46.7%; As per BMI, males (55.42%) were comparatively more overweight than females (41.96%). Abdominal obesity prevalence was more in females (83.76%) than in males (62.24%).
Conclusion
Obesity and abdominal obesity is a growing major health issue globally. As compared to male, female have more common both obesity and abdominal obesity. So for living a healthy life we highly suggest to control weight, blood pressure, blood sugar level.

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EP162

Assessment of the reproductive system function, metabolic and immunological status in women with obesity and overweight

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Background
Obesity is an excess accumulation of adipose tissue in the body, characterized by impaired lipid and carbohydrate metabolism with subsequent pathological changes. The purpose of this study was to investigate the functioning of the reproductive system, metabolic and immunological status in women of reproductive age with obesity and overweight.
Methods
We examined 110 women of reproductive age including 60 patients with obesity (group I), 25 overweight patients (group II). The control group consisted of 25 individuals without impaired body weight (group III). Evaluation of the levels of leptin, 25(OH)D, triglycerides, cholesterol, index–HOMA were performed. The concentration of cytokines (IL–6, 8 and TNF– α) was determined in serum by ELISA.
Results
In obese women, menstrual dysfunction, such as amenorrhea, dysmenorrhea, abnormal uterine bleeding, was observed in 43.3% vs 28.0% in the group of overweight women. Decrease in reproductive ability, such as subfertility and infertility, were established in 38.3% of women with obesity, vs – 24.0% of patients with overweight . Primary forms of obesity were accompanied by the most significant metabolic and immunological disorders (Table 1): severe 25(OH)D deficiency, dyslipilemia, impaired carbohydrate metabolism, and the pathological functioning of immune system (increased levels of Il–6, 8, TNF–α) which correlated with hyperleptinemia.
Conclusion
Obtained results show that obesity is a serious medical problem because it is accompanied by significant metabolic and immunological disorders, which indicates the need for their correction in order to normalize the functioning of woman's reproductive system.

Table 1 The correlations between the level of Leptine, metabolic and immunological parameters.

Group of patients	Parameters	Spearman's rank correlation coefficient, *r*
I	Leptine/ 25(OH)D	+ 0, 642
	Leptine/ Index–HOMA	+ 0, 608
	Leptine/ triglycerides	+ 0, 553
	Leptine/ cholesterol	+ 0, 534
	Leptine/ IL–6	+ 0, 403
	Leptine/ IL–8	+ 0, 508
	Leptine/ TNF–α	+ 0, 582
II	Leptine/ 25(OH)D	+ 0, 642
	Leptine/ Index– HOMA	+ 0, 628
	Leptine/ triglycerides	+ 0, 428
	Leptine/ cholesterol	+ 0, 518
	Leptine/ IL–6	+ 0, 628
	Leptine/ IL–8	+ 0, 428
	Leptine/ TNF–α	+ 0, 481

Note: If the value of the Spearman's rank correlation coefficient (r) <0, 3 – weak link, from 0, 31 to 0, 5 – moderate, >0, 5 – significant.

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EP163

Bariatric surgery : About 10 cases

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Introduction
Bariatric surgery is the treatment which has shown the most important effectiveness in terms of weight reduction, improvement of co morbidities, quality of life and mortality on the long term, in the case of massive obesity and obesity associated with co–morbidities. The purposes of our study: clarify the place of bariatric surgery in the treatment of obesity, define the criteria of selections of patients.
Material and methods
It's a retrospective study of ten patients who underwent bariatric surgery over a period of 1 year, from 1 April 2016 to 31 March 2017 at the service of general surgery in the Avicenna military hospital of Marrakech.
Results
The average age of patients was 33.7 years, a net predominance of women with 90% and a sex ratio of 0, 11. The mean BMI of our patients was 45.15 kg/m^2 with extremes ranging from 40.67 to 54 kg/m^2. Our patients followed a standard care pathway, with a multidisciplinary assessment including a consultation in endocrinology, in psychiatry and in gastroenterology. Pre–operative assessment diagnosed comorbidities related to obesity, in our study the results were: dyslipidemia 50% cases, Obstructive Sleep Apnea Syndrome 40% cases, type 2 diabetes 30% cases, NASH 60% cases, ischemic heart disease 10% cases, hypertension 10% cases. All patients received a coelioscopic approach. The main surgery technique was the sleeve

gastrectomy. The surgical time averaged 2 h17 minutes with extremes ranging from 1 h 40 to 2 h 50 minutes. The postoperative period was uneventful for 9 patients; one patient has an infectious peritonitis, re–operated J 3 after the sleeve, it evaluated to a multiple organ failure, we deplore the death of the patient at J5. The hospital stay duration averaged 13 days with extremes ranging from 5 to 25 days.
Conclusion
These benefits of bariatric surgery are to compare with the immediate and late complications and the peri–operative mortality risk, hence the interest of an optimal preoperative evaluation, per operative monitoring and postoperative management of complications.

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EP164

Prediction of Vitamin D receptor gene expression in visceral and subcutaneous adipose tissue in adults with excess weight

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In the current study, we aimed to illustrate determinants of VDR gene expression in visceral and subcutaneous adipose tissues among obese and morbidly obese adults. We gathered visceral and subcutaneous adipose tissues during an elective abdominal surgery form 33 morbidly obese (body mass index (BMI) >40 kg/m^2) and 23 obese (BMI = 30–40 kg/m^2) participants who were free of diabetes. Before the surgery, dietary intake, physical activity, anthropometric indices, and biochemical variables were collected. The gene expressions VDR in visceral and subcutaneous adipose tissue were assessed by Real–Time PCR. Multiple linear regression models were used to examine predictors of VDR gene expression among weight–based categorized participants after adjusting age, BMI, WC, 25(OH)D, HOMA–IR, calcium intake, and physical activity. The mean age of the obese and morbid obese was 42.3 and 36.7 years, respectively) and BMI of the obese and morbid obese was 34.4 and 47.7 kg/m^2. There was no significant deference between obese and morbidly obese participants in mean VDR gene expression in visceral and subcutaneous adipose tissues. Among obese participants, 25(OH) D (β = –0.103, P = 0.036) was negatively, and BMI (β = 0.292, P = 0.052) and HOMA–IR (β = 0.285, P = 0.052) were positively associated with VDR mRNA levels in visceral adipose tissue. In morbidly obese participants, the independent positive predictors of VDR gene expression in visceral fat were BMI (β = 0.309, P = 0.007) and HOMA–IR (β = 0.362, P = 0.004), and negative predictors were 25(OH)D (β = –0.114, P = 0.042) and calcium intake (β = –0.307, P = 0.008). Our findings suggested that 25(OH)D concentration is the fundamental element of VDR gene expression in visceral fat which by increasing fat depots, the subsequent insulin resistance became another predictor of VDR gene expression. Further studies will be required to unravel the physiological consequences of the different adipose tissue response of VDR gene expression depending on the degree of obesity and its relevance in clinical practice, as well as to confirm the role of VDR in glucose hemostasis.

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EP165

Secular trend in dietary patterns of iranian adults from 2006 to 2017: Tehran lipid and glucose study

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Background
By focusing on nutrition transition in the Middle East and North Africa, this study aim to investigate the general structure and secular trend of dietary patterns extracted from the Tehran Lipid and Glucose Study (TLGS) and adherence to these dietary patterns among Iranian population from 2006 till 2017.
Methods
We investigated on four examination surveys of TLGS including survey 1 (2006–2008), survey 2 (2009–2011), survey 3 (2012–2014), and survey 4 (2015–2017). The dietary intakes was gathered by a validated and reliable food frequency questionnaire. Generalized Estimating Equations was used to assess secular trends in anthropometric, biochemical, and dietary variables across the study period. To identify general structure and secular trend of dietary patterns during each survey, principle component analysis (PCA) and *K*–mean cluster analysis were used, respectively.
Results
After adjusting for potential confounders including age, sex, body mass index, and total energy intake, the carbohydrate and protein intake gradually increased and the total fat intake decreased during study period (P–value <0.001); however total energy intake remained stable. During the study period, participants consumed notable less refined grain, solid fat, dairy products, and simple sugar. Snack and dessert consumption increased and meat intake had no significant changes during a decade (all *P*–values <0.001). Three dietary patterns were extracted buy using PCA including: *Healthy dietary pattern* characterized by higher intake of vegetable, fruit, dairy products, liquid oil, nuts and seeds, and honey and jam, Western dietary pattern featured by refined grain, solid fat, meat, snack and dessert, potato, and soft drink, and the Mixed dietary pattern highlighted by tea and coffee, and simple sugar. Based on cluster analysis, 27.8% of participants in survey 4 followed a Western dietary pattern, and 34.1% followed the Mixed dietary pattern. The Healthy dietary pattern was stable among study population during the last decade.
Conclusions
The structure and the type of foods that population have chosen to eat had changed since 2006. And a new secular trend in dietary patterns including a stability of *Healthy* dietary pattern, a decline of the *Western* dietary pattern and an increase in the *Mixed* dietary pattern was presented in our investigation.

Keywords: dietary patterns, secular trend, nutrition transition, factor analysis, adults, TLGS.
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EP166

Bacterial metabolism in the colon and food behavior hormones in drug therapy of obese patients.

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As known, the number of obese people in the world exceeds 50% of the total population. ☪ search the causes of obesity development many researchers pay attention to metabolites of intestinal microflora among which the main ones are short–chain fatty acids (SCFA): acetate (C2), propionate(C3), butyrate(C4). Hormones of food behavior produced by visceral adipose tissue (leptin) and cells of the gastrointestinal tract (ghrelin) also play an important role in the development of obesity
Objective
To evaluate the activity of microbial metabolism in the colon in comparison with changes in hormonal status in obese patients before and after therapeutic weight correction.
Materials and methods
The study included 17 obese patients (7m / 10f, mean age 45.7±6.2 y; BMI 36.2±03.4 kg/m^2). Patients received monoamine reuptake inhibitor in the background of hypocaloric diet. Fecal SCFA were determined by GLC–method. Leptin and ghrelin were determined using the ELISA method.
Results
The total concentration of SCFA (TSCFA) in patients before treatment varied widely (5.1–14.8 mg / g) and averaged 9.7+3.1 mg/g, (vs norm 10.6+2.4 mg/g, NS). The spectrum of metabolites showed a marked decrease of conc. C4 ($p<0.05$ vs norm) and increase of conc. C3. Leptin and ghrelin concentrations in the blood were significantly increased: 20.2±7.1 ng / ml and 68.8±18.3 ng / ml.
After therapy BMI was decreased from 36.2±3.4 kg/m^2 to 33.1±4.6 kg/m^2 and the structure of fecal metabolites underwent significant changes: conc. of C 2 was decreased. (6.43±2.86 mg / g vs 4.771.26, $P<0.05$) and increased C 3 (1.94±0.78 mg /g vs 2.35±0.58, $p<0.05$) and C4 (1.23±0.27 mg / g vs 1.65±0.78, $P<0.05$). It is likely that these modifications of the metabolite structure cause an upward trend of leptin levels (20.2±7.1 ng

/ ml vs 25.7±8.3 $P=0.07$), since C3 and C4 have been shown to stimulate leptin production (Xiong Y., 2004). An interesting fact is that there is a high degree of correlation between C3 and leptin ($r=0.643$, $r=0.05$) and TSCFA and leptin ($r=0.714$, $P=0.05$) only after treatment. There were no correlations with SCFA and leptin before treatment or with ghrelin and fecal SCFA.
Conclusion
Thus, low–molecular metabolites of the fecal microflora have a noticeable effect on the hormonal status of obese patients.

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EP167

Metabolic disorders and the state of the renin–angiotensin–aldosterone system in obese patients with resistant hypertension

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Background
The aim was to establish the features of metabolic disorders and the state of the renin–angiotensin–aldosterone system (RAAS) in obese patients with true and pseudo–resistant arterial hypertension (AH).
Material and Methods
The study included 200 patients with uncontrolled AH and obesity. Patients were initially prescribed dual antihypertensive therapy. Those patients who did not reach target blood pressure (BP) levels after 3 months on dual therapy were additionally assigned a third antihypertensive drug. Of the 98 patients who were assigned triple therapy, 48 patients did not reach target BP (27 patients had pseudo–resistant and 21 patients had true resistant AH). These patients were additionally prescribed a fourth antihypertensive drug (spironolactone). The effectiveness of the treatment was evaluated 6 months after the start of antihypertensive therapy.
Results
After 6 months of therapy, unlike patients without resistance, individuals with resistant AH differed more pronounced metabolic disorders and higher activity of the RAAS. Patients with true resistance differed from pseudo–resistant patients with significantly lower body mass index (BMI); in the absence of differences in BP levels, lipid and carbohydrate profiles, patients with true resistance had significantly higher levels of aldosterone, higher adiponectin levels, and lower leptin level.
Conclusions
Obese patients with true resistance differed from pseudo–resistant patients with significantly lower BMI, higher aldosterone levels, and less pronounced adipokines imbalance.

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EP168

Evaluation of anxiety–depressive disorders in patients with metabolic syndrome

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In recent years, there has been an increase in patients with metabolic syndrome (MS), which is an urgent medical problem. The severity of the clinical manifestations of MS affects the quality of life of patients, while reducing physical and mental health. Obesity leads to anxiety and depressive disorders, neurosis–like conditions, which contributes to a worsening prognosis of the underlying disease.
The aim of the work was to assess the level of anxiety, depression and quality of life in patients with metabolic syndrome.
Methods
30 patients with MS and 35 healthy volunteers were examined at the clinic of the Research Institute of Medical Problems of the North. Patients were examined, anthropometric indicators were determined (waist circumference, body weight, BMI) with an assessment of the quality of life (questionnaire SF–36, Russian version, Institute of Clinical and Pharmacological Research, St. Petersburg). The level of anxiety and depression was determined by the hospital anxiety and depression scale HADS (The hospital Anxiety and Depression Scale Zigmond A.S., Snaith R.P.).
Results
Most indicators of quality of life were statistically significantly different in patients with MS relative to the control group. A decrease in the average level of the parameters "physical functioning" by 17.3% ($P<0.05$), "role–based functioning" by 31% ($P<0.05$), and "general health" by 11.3% ($P<0.05$), "vitality" by 13% ($P<0.05$), "emotional functioning" by 50.1% ($P<0.05$). The level of anxiety and depression in patients with MS corresponded to a subclinically expressed level, the level of depression exceeded the value of the control group by 18%.
Conclusion
Patients with MS are characterized by a decrease in quality of life indicators, subclinically expressed anxiety / depression. According to MAPI Research Institute, the goal of any treatment is to improve the quality of life of patients to the level of healthy individuals, therefore, for patients with MS, along with pathogenetic therapy aimed at weight loss, correction of psychological disorders is required, which will reduce the level of anxiety–depressive disorders and improve quality of life.

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EP169

Peripheral cannabinoid–1 receptor blockade potentiates the anti–obesity and anti–diabetic effects of GLP–1 mimetics

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Obesity and type–2 diabetes (T2D) represent a global health crisis. However, only a few, and often sub–effective pharmacological tools are available to treat these disorders. Though beneficial for glycemic control, GLP–1 receptor (GLP–1R) agonists show scarce weight–lowering and insulin–sensitizing efficacy.
New molecules able to selectively block the activity of the cannabinoid receptor type–1 (CB1R) in peripheral organs have been recently developed. In preclinical animal models, these non–brain penetrant drugs lead to sizable weight–loss and a global improvement in the multi–faced complications of obesity, including insulin resistance. These peripheral agents can bypass the known neuropsychiatric side–effects observed with brain–penetrant CB1R blockers.
Of note, GLP–1 release, and possibly its activity, may be negatively influenced by CB1R signalling, which implies that pharmacological inhibition of CB1R may be used as an effective approach to amplify the therapeutic benefits achieved with GLP–1R agonism.
Using genetic murine models with loss of CB1R or GLP–1R function, we found that these two metabolic receptors drive changes in food intake and body weight control via reciprocal functional interactions. CB1R knockout mice are more sensitive to the hypophagic effects of a GLP–1R agonist while a peripheral pharmacological blocker of CB1R (JD–5037) has blunted ability to lower body weight and food intake in mice lacking GLP–1R.
Such vicious interaction can be corrected pharmacologically. In diet–induced obese mice, the co–administration of JD–5037 with different types of GLP–1R agonists, including semaglutide, leads to more potent effects against obesity, insulin resistance, systemic dyslipidemia, and non–alcoholic fatty liver disease, relative to monotherapies. These benefits result from hypophagia, heightened systemic energy dissipation, and improved hepatic insulin action.
Thus, peripheral CB1R blockade may represent an effective strategy to safely amplify the anti–obesity and anti–diabetic efficacy of currently available GLP–1R agonists. Pharmacological co–targeting of CB1R and GLP–1R may help close the still–too–large gap between the anti–obesity efficacy of the available pharmacological tools relative to the efficacy of bariatric surgery, a procedure which has its risks.

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EP170

Evaluation of liver fibrosis in patients with diabesity

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Background
NAFLD(non–alcoholic fatty liver disease) includes; non–alcoholic fatty liver(NAFL), non–alcoholic steatohepatitis (NASH) and its complications (fibrosis, cirrhosis and hepatocellular carcinoma). These diseases are currently the most common cause of liver disease in western countries, due to the obesity and DM2 epidemic. There are scores that determine the risk of liver fibrosis in a non–invasive way.
Aims
To determine the prevalence of liver fibrosis diagnosed by FIB4 score, NAFLD fibrosis score and Hepamet fibrosis score in patients with morbid obesity. To evaluate differences in the risk of fibrosis in patients with morbid obesity with or without DM2.
Methods
Cross–sectional observational study of a sample of 95 high–risk obesity patients. Anthropometric variables (weight, size and BMI), analytical variables (glucose, insulin, AST, ALT, albumin and platelets) and non–invasive markers of liver fibrosis (FIB4, NAFLD, Hepamet) were collected. The risk of fibrosis was compared with the presence or absence of DM2.
Results
95 patients; 73.7% are women and 24.2% had DM_2. Mean age 44.22 (DE 8.34) years, weight 122.4 (RIC 84) Kg, BMI 45.82 (DE5.22) kg/m^2. 94.7% of patients have FIB4 <1.30 (without fibrosis or mild fibrosis); 3.2% FIB4 1.30–2.67 (undetermined) and 2.1% FIB4 >2.67 (advanced fibrosis). 28.4% of patients have NAFLD <–1.45 (without fibrosis or mild fibrosis), 65.3% NAFLD –1.45–0.675 (grey area) and 6.3% NAFLD >0.675 (advanced fibrosis). 85.1% of patients have Hepamet <0.12 (without fibrosis or mild fibrosis), 9.6% Hepamet 0.12–0.24 (Grey area) and 5.3% Hepamet >0.24 (advanced fibrosis). The risk scores for fibrosis in patients with obesity and DM_2 are reflected in Table 1.

Table 1

	SCORES	Diabetes	No diabetes	*P*
NAFLD	Without fibrosis or mild fibrosis	4, 3 %	36, 1 %	<< 0, 001
	Grey area	78, 3 %	61, 1 %	
	Advanced fibrosis	17, 4 %	2, 8 %	
	Total	100 %	100 %	
FIB4	Without fibrosis or mild fibrosis	95, 7 %	94, 4 %	0, 34
	Undetermined	4, 3 %	2, 8 %	
	Advanced fibrosis	0 %	2, 8 %	
	Total	100 %	100 %	
Hepamet	No fibrosis o leve	45, 5 %	97, 2 %	< 0, 001
	Grey area	36, 4 %	1, 4 %	
	Advanced fibrosis	18, 2 %	1, 4 %	
	Total	100 %	100 %	

Conclusions
There is a high prevalence of liver fibrosis in patients with morbid obesity. Patients with obesity and DM_2 have a higher risk of fibrosis estimated with NAFLD and Hepamet fibrosis score. In patients with obesity, DM_2, or other risk factors, the risk of liver fibrosis should be evaluated as it may condition the long–term prognosis.

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EP171

Gender differences in image dissatisfaction and distortion in brazilian patients referred to bariatric surgery

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Introduction
In Brazil, most patients referred to bariatric surgery are women. The literature indicates the occurrence of gender differences in body composition and body image perception.
Aim
To study body image perception and its relationship with body composition in Brazilian bariatric patients.
Methods
A total of 140 patients were evaluated using the Stunkard Figure Rating Scale (SFRS) and bioimpedance. Image dissatisfaction and distortion, body mass index (BMI), BMI excess (calculated as: [BMI – 25]), body fat percentage, muscle mass, and visceral fat were studied. Data from women and men were compared.
Results
114 women and 26 men were investigated. Seventy–six were studied before and 64 after bariatric surgery. There was no gender difference regarding age (41.73±11.52 vs 39.38±9.24 years, $P=0.3499$), prevalence of bariatric surgery prior to study inclusion (47.37% vs 38.46%, $P=0.5141$), time elapsed since surgery (27±32 vs 16±42 months, $P=0.4649$), BMI (37.78±8.6 vs 41.51±10.35 kg/m², $P=0.0573$) or visceral fat index (19.2±5.65 vs 18.8±6.27, $P=0.7784$). However, women had higher body fat percentage (46.48±7.25 vs 41.45±10.01%, $P=0.0053$) and men had higher BMI excess (18.10±10.97 vs 13.10±9.16 kg/m², $P=0.0170$) and muscle mass (40.88±5.58 vs 27.76±4.65 kg, $P=0.0001$). Based on SFRS, all subjects had image dissatisfaction (scores: women±3.7±1.6, men±3.2±1.3, $P=0.1648$), and women had higher scores of image distortion (0.99±0.86 vs 0.62±0.70, $P=0.0391$). The multiple regression model for the determinants of the dissatisfaction indicated BMI excess as the main influence ($r^2=0.8584$, $P=0.0346$), while the model for distortion suggested the impact of muscle mass ($r^2=0.3322$, $P=0.0032$).
Conclusion
Gender differences in body composition are in accordance with the literature. Most subjects in this study were women, the subgroup with the higher prevalence of image distortion, which may have contributed to their higher prevalence of obesity and, consequently, referral to surgical treatment. Present in all subjects, image dissatisfaction could have been a trigger for the search of medical treatment.

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EP172

Is endothelial dysfunction the main issues in prediabetes as predictor for cardiovascular diseases?

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Background
The frequency of prediabetes is increasing as the prevalence of obesity rises worldwide. Hyperglycemia, insulin resistance, inflammation and metabolic derangements associated with concomitant obesity cause endothelial dysfunction in prediabetics, leading to increased risk of cardiovascular and renal disease.
Objective
To get a general perspective on the complex relationship between cardiovascular diseases onset, and pre–diabetes
Methodology
100 obese patients compared to 45 normal controls The study was conducted between June 2018 and april 2018 .All subjects were submitted to history taking, clinical examination including wasit circumference, BMI, Hb A1c, Fasting blood glucose, lipid profile, carotid artery duplex and Brachial artery flow media dilation (FMD)
Results:
Mean age of our patients was 30±0.3 years, BMI :30.26±3.08, cholesterol: 240±22.1 mg/dl, triglycerides : 105±12.2 mg/dl, LDL :140.7±32.1 mg/dl, HDL : 38.45±9.5 mg/dl, and A1C : 5.95±0.2. There was statistically significant difference in Carotid intimal media thickness between prediabetic and controls (0.10±0.02/0.08±0.01) (P±0.01). However, there was

no statistical significance difference between patient and control regarding FMD: (13.40±12.59 /8.63±1.01) (P=0.26).
Conclusion
Screening for prediabetes and early management is of utmost importance for prevention of cardiovascular morbidity as it is an incipient for premature atherosclerosis, endothelial dysfunction follow changes in CIMT, which highlights that screening of CVS in prediabetics should be done by CIMT and not by FMD.

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EP173

Malignant insulinoma in an adult female: diagnosis and treatment challenge. A case report

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Insulinoma represents one of the most encountered neuroendocrine tumors, but only 4–14% is malignant. The diagnosis is suggested by high serum insulin levels during spontaneous or induced episodes of hypoglycemia and often invasion of lymph nodes and liver metastasis. A 55–year–old female was referred to our center after an episode of hypoglycemia during strumectomy for multinodular goiter. Further questioning revealed few years of Metformin treatment for hyperglycemia, which was stopped after repeated hypoglycemic episodes (3–4/week, Gl min=20 mg/dl) with remission after fast–acting carbs leading to an increase of 40 kg body weight in the last 5 years. Her family history was positive for pancreatic cancer. Post–strumectomy, the patient developed Gerhardt syndrome and hypoparathyroidism requiring daily i.v Calcium infusion. The 72–hour fast was stopped for symptomatic hypoglycemia (Gl=41 mg/dl) and an glycemia/insulinemia=2.34. The A1c=4.5% confirmed the presence of frequent hypoglycemic episodes. The CT scan revealed a tumor in the uncinate process of the pancreas for which enucleation was performed. Microscopic view was consistent with malignant insulinoma. After surgery, the patient became euglycemic with an A1c of 5.6% after 3 months and 10kg weight loss.
Despite its low incidence, the presence of insulinoma must be suspected in every person with repeated hypoglycemia after exclusion of other causes. The imaging studies and the histopathological exam are mandatory in order to establish localization and its malignant features.

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EP174

Type 2 diabetes mellitus and pancreatic cancer in related family

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The lifetime risk of pancreatic cancer for the average individual without a family history of pancreatic cancer is approximately 1%. Individuals with a family history of pancreatic cancer are at an increased lifetime risk for developing pancreatic cancer. This risk is likely higher for individuals from a family with FPC. The following cancer risk estimates are generalized and should be interpreted with caution since the actual risk for each individual may be different:We received a case study of two siblings of one family. The older brother was diagnosed with Type 2 Diabetes in 2017 and began insulin therapy at age 72. After one year of treatment with insulin therapy, he had symptoms such as nausea, vomiting, pruritus, weakness, weight loss. While there was no fluctuation of glycemia, with HBA1c=7%. At this moment all necessary examinations are done and results were magnetic resonance with pancreatic Ca and pulmonary meta. Ca 19–9=700.6 .After six months the patient died. In 2018 was present his brother aged 70 with typical signs of Type 2 Diabetes with polydipsia polyuria syndrome and weight loss. Glycemia=400 mg/dl and HbA1c=12%. Insulin therapy was started. During one year presented with satisfactory parameters. glycemia and HbA1C. After one year the same signs as brother, nausea, vomiting, headache, generalized pruritus began. Necessary examinations are performed and magnetic resonance results pancreas Ca and Ca19–9=1000. Actually the patient is undergoing to radiotherapy and follow–up by the oncologist. In this case, we observed that the disease appeared to be preceded by type 2 diabetes mellitus over the age of 70 and with the same symptoms. Familial pancreatic cancer (FPC) is a term to describe families with an abnormally high rate of **pancreatic cancer**. Ductal adenocarcinoma of the pancreas, which is the most common type of pancreatic cancer, starts when healthy cells lining the pancreatic ducts change and grow out of control, forming a tumor. The pancreas is a pear–shaped gland found in the abdomen between the stomach and spine. The gland makes enzymes that help the body digest food. It also makes hormones, such as insulin, that help control blood sugar. Families are considered to have FPC if there are at least 2 members of the family with pancreatic cancer who are first–degree relatives, such as a parent, child, or siblings of one another.

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EP175

Very low HbA1c– a case presentation

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Background
We present an interesting case of a 56 year old male who, during pre–operative work up, was found to have a very low HbA1C 3.1% (10 mmol/mol). The patient was also noted to have mild thrombocytopenia, raised bilirubin and alanine aminotransferase and moderate splenomegaly on CT scan, with otherwise normal appearance of remaining abdominal viscera. His past medical history included alcohol excess (60–80 units/week), he was not diabetic and was taking Aspirin and Atorvastatin. It was felt his HbA1c was artefactually low due to increased red cell breakdown associated with splenomegaly.
Discussion
HbA1c is a validated, internationally recommended test for the diagnosis of diabetes, though HbA1c can become falsely lowered in clinical scenarios which lead to increased red cell turnover and therefore decreased opportunity for glycation of HbA1. Several population based cohort studies have investigated the link between very low HbA1c and mortality outcomes in non–diabetic adults, with varied results. Most agree there is a statistically significant link between very low HbA1c and all–cause mortality, though this becomes insignificant when adjusted for lifestyle and co–morbidity factors, and indeed the well–known "J–shaped curve" effect was subsequently accounted for when additional adjustment for liver function derangement was applied to their data set. Whilst very low HbA1c may not be an independent risk factor for increased mortality, there is potential for the finding to be a surrogate marker of increased all–cause mortality, and the authors would suggest this finding should not be quickly discounted as insignificant, but should prompt a thorough multi–systems assessment for potential underlying pathology. The patient in this case awaits Haematological work up of his splenomegaly, the cause of which has not yet been defined.

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EP176

Diabetic ketoacidosis and continuous glucose monitoring – a case report

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Introduction
Diabetic ketoacidosis (DKA) is characterized by the triad – ketonemia, metabolic acidosis and hyperglycemia. It is typically associated with type 1 Diabetes Mellitus (T1D) and the most common culprits are infections and poor therapeutic compliance.
Clinical Case Description
The present case deals with a 25–year–old female patient, with T1D diagnosed in 2008, without microvascular or macrovascular complications. She presented with poor metabolic control (Haemoglobin A1c (HbA1c)=11.7%) under functional insulin therapy with insulin glargine and aspart, guided exclusively by reading of the Flash Glucose Monitoring (CGM) system, which recorded values within glycemic goals.

The patient was admitted to the Emergency Room (ER) with DKA, exhibiting hyperglycemia of 578 mg/dl, severe metabolic acidemia (pH 6.9 and HCO3– not measurable – low) and ketonemia of 4.4 mmol/l. Other triggering factors were excluded.
This DKA was treated with fluid therapy and IV infusion of rapid acting insulin. Clinical and analytical resolution of DKA was achieved, progressing with oral tolerance and resuming subcutaneous insulin regimen. However, due to phlebitis of the left forearm in a site of arterial puncture and acute cystitis, DKA recurred. Standard treatment of DKA was reimposed, along with amoxicillin/clavulanic acid. After this recurrence, the patient exhibited flexion of the 4th and 5th fingers of the left hand, decreased strength in the ipsilateral hand and absence of distal pulses, consistent with left brachial artery and upper–extremity deep vein thrombosis which was treated with thromboembolectomy. At discharge, she presented good glycemic control under insulin pump therapy.
Five months later, the patient developed paracentral acute middle maculopathy, with hypovision of the left eye. For this reason, a genetic study was conducted, compatible with high prothrombotic risk (heterozygous Factor V Leiden mutation; homozygous methylenetetrahydrofolate reductase (MTHFR) mutation; Plasminogen Activator Inhibitor–1 (PAI–1) 4G/5G promoter polymorphism). Treatment with hyperbaric oxygen therapy was performed, with complete visual recovery along with rivaroxaban. Currently, under insulin perfusion pump, she presents sustained metabolic control (HbA1c=6.2%).
Conclusion
This particular case alerts us to several risks: self–monitoring of DM1 exclusively based on a flash system, failure in the self–awareness of symptoms, possibility of recurrent DKA and, finally, thrombotic events as a serious and rare complication of DKA, in genetically predisposed patients.

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EP177

Effect of pilgrimage on metabolic syndrome among diabetic patients

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Background
Hajj is one of the five pillars of Islam and is a must–do for all adult Muslims once in their life provided they are able to do it. It's estimated that pilgrims with diabetes could exceed 220000/year. Patients with diabetes are at a great risk of illness due to the nature of the disease and the altered daily routine (overcrowding, inadequate nutrition, poor access to drinking water, hot weather and physical exertion).The primary aim of this study is to evaluate the effect of pilgrimage on metabolic syndrome.
Material and methods
Cross–sectional study covered 43 diabetic patients from the city of Sousse, intending to perform the pilgrimage during 2019. The evaluation was made before and after pilgrimage and included clinical examination and biological assessment.
Results
The study covered 43 patients : 25 women (58.1%) and 18 men (41.9%) with a gender ratio (W/M)=1.8, all with type 2 diabetes. The mean course of diabetes was 12, .±9.3 years . Thirty patients were on oral anti–diabetic drugs, 2 patients were on dietary rules alone and the rest were on insulin (26.3%). The average of glycated hemoglobin (HbA1c) was 7.9±1.3 %. Fasting blood glucose, Cholesterol and LDL cholesterol significantly decreased after pilgrimage (7.8±2.88 vs 69±2.55, 4.2±1.03 vs 3.7±1.01 and 0.92±0.34 vs 0.7±0.33, respectively, $P=0.05$). Also most patients had lost weight after pilgrimage (the average of Body mass index significantly decreased 30.0±5.45 vs 28.9±4.11, $P=0.05$) with a significant decrease in waist size.
Conclusion
Although the altered daily routine of patients with diabetes during the pilgrimage, an improvement in most parameters of metabolic syndrome was observed. This enhancement is mainly due to physical activity.

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EP178

Otogenic thrombophlébitis : A rare complication in diabetic patients

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Background
Otogenic cerebral thrombophlebitis is a rare intracranial complication of otitis media in the modern age of antibiotic treatment, but it is potentially a dangerous complication spatially in immune depressed patients with diabetes.
Aim
To discuss the clinical features of this complication and to analyze the impact of diabetes on its evolution as well as the management of this entity.
Methods:
We conducted a retrospective study on 10 diabetic patients with otogenic cerebral thrombophlebitis diagnosed and treated in ENT Departement of Farhat Hached Hospital from 1995 to 2019.
Results
10 poorly controlled diabetic patients were enrolled :8 men and 2 women with a mean age of 35 ans (extremes from 11 to 77 ans). The mean delay of consultation was 27 days (extremes from 7 days 3 months). Clinical presentation was made of otlagia in all patients and otorreha in 9 patients. The etiology was acute otitis media in 8 cases and cholesteatoma otitis media in 2 cases. All patients were assessed by CT Scan with contrast .The thrombosis was located in lateral sinus in 5 cases, sigmoide sinus in 2 case, Cavernous sinus in 1 case, and internal jugular vein in 30% of cases. The thrombphlebitis was on the right side in 3 cases, on the left side in 6 cases and bilateral in 1 case. The occlusion was total in 4 cases and partial in 6 cases. It was associated to other complications : mastoiditis in 5 cases, extradural empyema in 2 cases and cerebral abcess in 3 cases. The treatment was based on insulinotherapy, antibiotherapy and anticoagulation for 15 days to 3 months in alla cases. Surgical management was completed in 5 cases.
Conclusion
Otogenic cerebral thrombophlebitis in a rare and seriuos complicaion, more common in diabetic patients who are immunodepressed. Its diagnosis is based on CT Scan. It requires well controlling diabetes, antiobiotheray, anticoagulation with surgical drainge.

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EP179

Gradation of podiatric risk in a population of patients with diabetes

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Introduction
The American Diabetes Association (ADA) recommends an annual foot screening of patients podiatric risk for ulceration and amputation, to take effective preventive measures. However, the gradation of the podiatric risk remains insufficient, particularly in Tunisia, where epidemiological references remain missing. The aim of this study was to classify a population of diabetic patients according to the grade of podiatric risk by referring to the recommendations of the International Working Group of The Diabetic Foot (IWGDF) of 2019.
Patients and methods
This is a prospective cross–sectional descriptive study of 100 patients with diabetes. Screening for diabetic neuropathy was done by the Semmes–Weinstein monofilament test (10g). Peripheral arterial disease was assessed by palpation of the peripheral pulses.
Results
The mean age was 54±12.9 years, The sex ratio was 0.78. Diabetes was type 2 in the majority of cases (78%). The average duration of progression of diabetes was 13.62±6.29 years. 78% of the population has been unbalanced. The prevalence of sensory neuropathy was 41%. That of peripheral arteriopathy was 18%. Grade 0 was the most frequent with a frequency of 59%. Only 4% of the population had grade 3. The frequences of Grade 1 and 2 were respectively of 21 and 16%.
Conclusion
The diabetic foot is one of the most expensive and difficult to manage complications of the diabetes. The gradation of the podiatric risk is a simple means of screening making it possible to identify the subjects whose risk is high.

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EP180

Risk assessment of patients with diabetes for foot ulcers in a tunisian population

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Introduction
Diabetic foot is a major health problem for people with diabetes mellitus. It can cause serious complications leading to lower extremity amputations. The aim of this study was to determine the prevalence and risk factors of foot complications among diabetic patients in Mahdia, Tunisia.
Methods
Detail history and examination including neurological and vascular assessment were performed in 150 patients with diabetes mellitus attending Tahar Sfar hospital and Ezzahra primary care center in Mahdia. Foot at risk was classified according to risk classification consensus of the International Working Group on the Diabetic Foot (IWGDF). The risk level was correlated with demographic and clinical features.
Results
The mean age of patients was 56.91±12.6 years with a range of 20 to 86 years. A low level of education was found in 76% of cases and patients had a history of hypertension (41.4%), high total cholesterol (46%). Smoking was found in 13.3% of cases. Half of patients were using oral medications, 28% were using insulin therapy and 21.3% were using both oral and insulin therapies. A medical history of hypertension was found in 41.4% of patients. Only 10% of diabetics had been screened for sensory neuropathy. Forty–three per cent of patients were in group 0 of the IWGDF, 37% in group 1, 15.3% in group 2 and 4% in group 3. Patients in higher–risk groups had longer diabetes duration ($P=0.045$).Risk was higher in the presence of diabetic neuropathy ($P=0.0001$), retinopathy ($P=0.000009$) and nephropathy ($P=0.02$). Patient's BMI, smoking did not have signifcant correlation with risk of diabetic foot ulcer.
Conclusion
Despite the low prevalence of foot ulceration and amputation among the study population, a substantial proportion had potential risk factors for foot complications.

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EP181

Prevalence and predictors for hypogonadism among tunisian type 2 diabetic patients with erectile dysfunction

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Introduction
Testosterone levels are frequently low in men with type two diabetes mellitus, and sexual symptoms are a prominent presenting feature for these men.
Objectives
The aim of this study was to determine the frequency of hypogonadism and related risk factors among Tunisian patients with type two diabetes mellitus and erectile dysfunction.
Methods
This cross–sectional study included a total of one hundred and thirty consecutive men with type two diabetes and erectile dysfunction who attended the Internal Medicine and Endocrinology Department, Monastir University Hospital, Tunisia. Erectile function was assessed using the International Index of Erectile Function score (IIEF). All the patients submitted the fully completed Androgen Deficiency in Aging Male (ADAM) questionnaire. Hypogonadism was defined as total testosterone < twelve nmol/l.
Results
Of the one hundred and thirty total patients, twenty one per cent exhibited decreased libido, and sixty–one per cent reported more than three symptoms of ADAM. Hypogonadism was present in forty one patients. Among these patients, hypogonadotropic hypogonadism was the most prevalent form (seventy per cent). Patients with hypogonadism had lower Index of Erectile Function score compared to those with normal total testosterone. Significant negative correlation was found between total testosterone and body mass index, waist circumference, androgen deficiency symptoms, and HBA1c. In logistic regression analysis, erectile dysfunction severity and HBA1c were statistically significant risk factors for hypogonadism.
Conclusions
Considering that hypogonadism is frequent in type two diabetic subjects with erectile dysfunction, an appropriate screening should always be performed in those patients in order to detect those who have low serum total testosterone level at any early stage and to supplement testosterone accordingly.

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EP182

The relationship between T2DM, nontoxic multinodular goiter and related osteoporosis/osteopenia

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Introduction
Pathological features of T2DM – change in β–cell mass, increased intestinal glucose absorption, glucagon secretion, gluconeogenesis, enhanced catecholamines, insulin resistance – features of hyperthyroidism as well. It is known that Insulin Like Growth Factor Binding Protein (ILGFBP) is related to high insulin (possible asymptomatic hypoglycemia) as well to function and growth of the thyroid, that's why there is increased risk that patients with T2DM will develop goiter and its associaed osteopenia/osteoporosis. It's evident that TSH effects directly on bone formation and bone resorption, via the TSH receptor on osteoblast and osteoclast precursors. Association of T2DM and thyroid dysfunction is a less explored area, which may answer to various mysteries of metabolic diseases.
Methods
Retrospective cohort study.
We have studied 51 T2DM patients with nontoxic multinodular goiter and osteoporosis/osteopenia – to understand development in time and analyse possible outcomes. Age (yrs) – 63.53±9.16; 30–60=15 (29.5 %); 60≤36 (70.5%); Sex– F=42 (82.5%); M=9 (17.5%); Duration: Diabetes – 10.69±6.405; <6 yrs=16 (31.3%); ≥6 yrs=35 (68.7%); Nontoxic Multinodular Goiter – 4.41±3.56; <6 yrs=11 (21.5%); ≥6 yrs=40 (78.5%); Osteoporosis (n20) ; 1.4±0.59; <6 yrs=20 (100%); Osteopenia (n31)– 1.25±0.85; <6 yrs=31 (100%); HbA1c(%) – 7.76±2.26; <7.5%=30 (58.8%); >7.5%=21 (41.2%); TSH (μIU/ml) – 0.74±0.45; <0.4=14 (24.5%); >0.4=37 (75.5%) ; vit.D3 (OH25) (ng/ml)=14.42±7.88; i–Ca(mmol/l)=1.2±0.14; BMI (kg/m^2) –30.61±5.40; Therapy– oral anti–diabetic drugs– 39(76.5%), combined (oral+insulin) anti–diabetic therapy – 12 (23.5%).
Results
Linear regression showed correlation between HbA1c and TSH (Goodness of Fit – R square– 0.3826, P value – <0.0001, 95% confidence interval – 0.07906 to 0.1700) ; Duration of T2DM and nontoxic multinodular goiter (Goodness of Fit – R square– 0.2125, P value – 0.0007, 95% confidence interval – 0.1147 to 0.3988) Duration of goiter and osteoporosis/osteopenia (Goodness of Fit – R square– 0.08001, P value – 0.0443, 95% confidence interval – 0.001542 to 0.1192).
Conclusion
Current study shows that there is significat correlation between duration of T2DM and development of Thyroid Dysfunction and association between HbA1c levels and TSH is evident. We consider patients with T2DM as a high risk to Thyroid Dysfunctions, especially patients with possible asymptomatic hypoglycemic events and recommend to screen frequently. Thyroid Dysfunction itself effects bone health. The interface between Thyroid malfunction owing to diabetes is a matter of further investigation.

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EP183

Polycysticovary syndrome (PCOS) and type 1 diabetes : A report of two cases

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Introduction
PCOS is the most common endocrinopathy in adolescents and young women. Insulin–resistance and hyperinsulinism are its primary mechanisms,

which explains the frequency of its association with type 2 diabetes. But not many studies have been interested in the association between PCOS and type 1 diabetes.
Patients and methods
Two type 1 diabetes patients have been included in this study, aged respectively 17 and 16. The first patient had been treated by human insulin, whereas the second patient had been treated with analogues of insulin. The duration of the diabetes was of 5 and 15 years respectively and was uncomplicated in both patients. Both patients had menstrual irregularities such as spaniomenorrhea and secondary amenorrhea. Upon clinical examination, the first patient had grade 1 obesity and the other patient was slightly over weigh twith an android fat distribution. Both patients have been diagnosed with PCOS, based on Rotterdam criteria including signs of hyperandrogenism such as acne, seborrhea and a mild hirsutism, a hypertestosteronemia and polycystic ovaries on ultrasonography, after having eliminated the differential diagnosis. The therapeutic approach for both patients was dietary adjustment and a progestogen.
Discussion and conclusion
in type 1 diabetes mellitus, the prevalence of pcos is 24 to 33%. but this disease remain sunder–diagnosed. the physiopathological mechanism of this association has not been fully understood. the exogenous hyperinsulism by insulin overdose has been incriminated, which is probably the case for our two patients. the risks linked to type 1 diabetes such as neoplasic diseases, reproductive difficulties, metabolic and cardiovascular repercussions are increased by pcos. nowadays, in the absence of clea rrecommendations for the treatment of pcos in type 1 diabetes, the therapeutic approachre mains poorly codified.

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EP184

Evaluation of selectins, membrane potential and antioxidant vitamins on diabetic patients attending general hospital, owerri

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Aim
The levels of serum Selectins (P and E–Selectin), membrane potential and antioxidant vitamins were determined in diabetic patients attending General Hospital Owerri, Nigeria.
Materials and methods
A case control study involving 600 persons living with diabetes between the ages of 20 and 60 years attending General Hospital Owerri. Also, 600 apparently healthy persons within the ages of 20 and 60 years served as control. Fasting venous blood was collected for the determination of serum P–selectin, E– selectin, membrane potential, vitamins C and E. The serum selectins and vitamins were estimated using enzyme linked immunoabsorbent assay (ELIZA). While membrane potential was calculated using Nerst equation. The Independent Student t test was used for statistical analysis.
Results
The levels of P–Selectin and E–Selectin were significantly higher in diabetes ($P<0.05$), when compared with the control. The levels of membrane potential, vitamin C and Vitamin E were significantly decreased in people with diabetes ($P<0.05$), when compared with the control.
Conclusion
The result suggests that diabetes could probably be associated with increased P–Selectin and E–Selectin levels which may be useful diagnostic tool for predicting the severity of diabetes. Also the decreased membrane potential could be linked to decreased energy while reduced vitamins in diabetes could be linked to oxidative stress.
Key words: P–selectin, E selectin, membrane potential, vitamin C and E.

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EP185

Complicated necrotizing otitis externa in diabetic patients

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Introduction
Necrotizing otitis externa (NOE) is an invasive infection. It may present with a variety of clinical findings. The most common symptoms are purulent otorrhea and exquisite otalgia resistant to analgesics. Diabetics are susceptible to microangiopathy that dulls pain perception thus predisposing them to severe complications of inctious disease.
Materials and methods
We reported ten cases of complicated necrotizing otitis externa in diabetic patients treated in ENT department of Tahar Sfar Hospital in Tunisia.
Non diabetic patients were excluded.
Results
Ten patients were diabetic occuring in 6 women and 4 men. The mean age was 64 years ranging from 58 years to 71 years. The average duration of diabetes follows up was over 10 years. All patients have received oral and local antibiotics before hospitalization. Symptoms were made of otalgia in all patients, otorrhea in 6 patients. Headache and temporo–mandibular joint pain were reported in two cases. Fever was observed in four patients. Four patients noted ipsilateral facial palsy. Stenosis of external auditory canal was observed in all patients Pseudomonas aeruginosa was t isolated in 9 cases and candidada albicans in one case. Computed tomography confirmed the NOE in all cases. CT scan showed also an extension to parapharyngeal space in 2 cases with a huge abcess in one case, to the rhinopharynx in one case, temporomandibular arthritis in two cases, lysis of the skull base in one case, lysis of the facial canal in two cases, sigmoid sinus thrombosis in one case and jugular vein thrombosis in two cases. MRI was performed for two cases with extension to parapharyngeal space and to the rhinopharynx. Diabetic control worsened with the onset of invasive external otitis in all cases. Nine patients have received intravenous anti–pseudomonal medications. Antifungual therapy was conducted in one case. One patient had a drainag of retropharyngeal abcess. Heparin was not used for the cases of septic thrombosis. A regression of symptoms was observed in 8 cases and two patients had facial palsy as sequalae.
Conclusion
Necrotizing otitis externa remains a devastating infection due to its complications. Always think about it, especially in diabetics, in order to get adequate treatment in time and prevent complication. Adequate control of diabetes in association with antibiotic therapy must be started quickly to reduce morbidity and mortality.

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EP186

Complex rehabilitation of comorbid patient after acute myocardial infarction with type 2 diabetes mellitus and obesity

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Rehabilitation of comorbid patients after acute myocardial infarction (AMI) with concomitant diabetes mellitus type 2 (DM2) and obesity requires application of personalized medical programs involving non–pharmacological physical methods and effective pharmacological therapy of DM2. The aim of the clinical case presentation is a description of the experience of complex medical rehabilitation of the middle–aged woman in the early period of AMI on the background of DM2 and morbid obesity using modern methods of physical therapy and liraglutide.
Case description
Female aged 51 years old was hospitalized in in–patient rehabilitation department with the diagnosis of Coronary heart disease; AIM of the left ventricle with growth of ST of 19.12.2019 (the 8th day); Stenting of the right coronary artery at 19.12.2019; DM2; Morbid obesity. The woman complained of dyspnea, increasing fasting blood glucose (FBG) up to 12 mmol/l. *Survey data*: height 165 cm, weight 152 kg, BMI 55.8 kg/m^2, waist circumference (WC) 139 cm, hips circumference (HC) 143 cm, blood pressure (BP) 148/98 mm Blood panel and routine urine analyses were without any pathological changes. HbA1c 7.6%, serum FBG 9.1 mmol/l, total cholesterol (TC) 7.4 mmol/l, triglycerides (TH) 3.08 mmol/l, low density lipoproteins (LDL) 4.8 mmol/l, high density lipoproteins (LDL) 1.2 mmol/l.
Rehabilitation program
low–calorie diet, low–intensity laser exposure #10, cardiological complex of physical exercises in a gym #10, bike exercises in a gym #10, speleotherapy #10, low–intensity kinesiotherapy #10. Due to AIM metformin has been changed to liraglutide which was initiated in a dosage of 0.6 mg/day, followed by a dose increase of 0.6 mg/day per week up to a therapeutic dose

of 1.8 mg/day. The patient was discharged in 12 days to continue her recovery in out–patient department. *In 30 days*: shortness of breath significantly decreased and tolerance to physical loads improved. Body weight 145 kg, BMI 53.3 kg/m^2, WC 132 cm, HW 140 cm, BP 124/79 mm Hg. Serum FBG 5.3 mmol/l, TH 6.9 mmol/l, TG 3.03 mmol/l, LDL 4.4 mmol/l, LDL 1.22 mmol/l. *In 3 months*: actively works, no complaints, weight 139 kg, BMI 51.1 kg/m^2, WC 128 cm, HC 132 cm, BP 125/78 mm Hg. Serum FBG 5.1 mmol/l, TH 5.9 mmol/l, TG 3.01 mmol/l, LDL 3.52 mmol/l, LDL 1.36 mmol/l, HbA1C 6.5%.
Conclusions
This clinical case demonstrates the results of complex rehabilitation of the middle–aged woman with AIM on the background of DM2 and morbid obesity using physical therapy methods and hypoglycemic pharmacological therapy with liraglutide.

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EP187

Clinical presentation and course of hemichorea due to hyperglycemia: A case series

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Introduction
Acute hemichorea due to hyperglycemia has been reported in subjects with type 2 diabetes, type 1 diabetes, and a rare type of diabetes, maternally inherited diabetes and deafness. This condition was generally subsided after adequate glycemic control, and the recurrence of hemichorea was rarely reported.
Case report
We comprehensively reviewed clinical presentation and course of hemichorea in five elderly patients with type 2 diabetes (four women and one men). Age was 69–84 years and duration of diabetes was 1–35 years. Initial HbA1c levels were 9.3–13%. They had multiple comorbidities, hypertension (n=4), dyslipidemia (n=4), and chronic kidney disease (n=4). Three patients were previously prescribed insulin but had poor compliance. Four patients undertook brain MRI and one of them performed brain FDG–PET. Three out of four brain MRI showed high signal intensities of putamen in T1–weighted images. FDG–PET scan showed hypometaboism in the corresponding lesions. Metabolic derangement or vascular insufficiency might be the pathophysiology of hemichorea in this case. Duration of hemichorea was various from 10 days to 5 months. All of them were treated with multiple daily insulin injection, and four patients were treated with dopamine–receptor blockers. One patient's hemichorea was recurred after 2 months from the time when the first event was resolved. This patient was finally diagnosed with vasculitis and followed a grave course after treatment of immunosuppressant.
Discussion and conclusion
The prognosis of hemichorea due to hyperglycemia seemed to be good, and we can easily detect typical brain MRI findings. However, we should consider other cause of hemichorea such as vasculitis when the symptom was recurred after adequate glycemic control.

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EP188

Efficacy and safety of statin use in children and adolescents with familial hypercholesterolaemia: A systematic review and meta–analysis of randomized–controlled trials

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Objective
Statins are the mainstay of treatment for patients with familial hypercholesterolaemia (FH). The purpose of this study was to systematically investigate and meta–analyze the best available evidence from randomized–controlled trials (RCTs) regarding the efficacy and safety of statins in children and adolescents with FH.
Methods
A comprehensive search was conducted in PubMed, Scopus and Cochrane, up to July 10, 2019. Data were expressed as mean differences with 95% confidence intervals (CI). The I^2 index was employed for heterogeneity.
Results
Ten RCTs were included in the qualitative and nine in the quantitative analysis (1.191 patients, aged 13.3±2.5 years). Compared with placebo, statins led to a mean relative reduction in total cholesterol (TC), LDL–C, triglyceride and apo–B concentrations by –25.5% (95% CI –30.4%, –20.5%; I^2 91%), –33.8% (95% CI –40.1%, –27.4%; I^2 90%), –8.4% (95% CI –14.8%, –2.03%; I^2 26%) and –28.8% (95% CI –33.9%, –23.6%; I^2 83%), respectively. HDL–C was increased by 3.1% (95% CI 1.1% – 5.2%; I^2 0%). The effect on TC, LDL–C and apo–B seems to be potency–dependent. More than half of patients may achieve the LDL–C target with high–intensity statin dose (4–14% with low–to–moderate intensity). Baseline LDL–C concentrations do not seem to predict the lipid–lowering effect of statins. Statins were well–tolerated (no effect on growth or sexual development), with no significant differences in transaminase and creatine kinase levels compared with placebo.
Conclusions
Statins are quite effective in reducing TC, LDL–C, TG and apo–B and increasing HDL–C concentrations in children and adolescents with FH. No safety issues were seen with statin use.

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EP189

Risk of hospitalization for cardiovascular events associated with diabetes therapies in type 2 diabetes patients in lithuanian cohort

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Background
Type 2 diabetes (T2DM) is associated with increased risk of cardiovascular (CV) complications. Although evidence suggest SGLT–2 inhibitors and GLP–1 receptor agonists to have a protective effect on CV outcomes they are still not available as a second–line therapy in Lithuania because of costs.
The aim
To examine the risk of hospitalization for CV events associated with diabetes therapies in patients with T2DM.
Methods
Lithuanian National Health Insurance Fund database, covering the period 2012 – 2014 was used to extract all diabetes cases with demographic data, information on complications, concomitant diseases, hospital admissions, prescribed medications. T2DM patients were grouped according to diabetes treatment. Nearest neighbor propensity score matching included age, gender, hypertension, chronic kidney disease, established CVD, diabetes complications, use of statins and ACEI to match the groups. Hospitalization risk for CV complications (miocardial infarction (MI), coronary heart disease (CHD), heart failure (HF), transient ischemic attack (TIA), stroke) was compared between the groups.
Results
From 124416 DM cases extracted, we excluded T1DM, treatment changes or initiation after index period. Matching of remaining 75666 T2DM cases resulted in 7089 patients in each Diet, Metformin, Sulfonylurea (SU)/Insulin and Combination therapy group with similar age – 69 years, women – 62%,

established CVD – 58%, hypertension – 87%, use of ACEI – 64% and statins – 7%. About 14% had DM complications, polyneuropathy being diagnosed most commonly in 11% of patients. In SU/Insulin group 53% were on SU, in Combination therapy – 82, 31, 97, 13, 2 and 3% – were respectively on SU, insulin, metformin, DPP–4 inhibitors, thiazolidinediones and GLP–1 receptor agonists. Compared to Metformin risk ratio (RR) for hospitalization was 1.18 [CI 1.11, 1.25] with the highest RR for TIA 1.32 [1.04, 1.67] in Diet, 1.24 [1.17, 1.32] with the highest RR for MI 1.51 [1.36, 1.66] in Su/Insulin, 1.15 [1.09, 1.22] with the highest RR for stroke 1.29 [1.07, 1.55] in Combination therapy groups. Compared to Diet RR for hospitalization was 1.06 [1.00, 1.11] with the highest RR for MI 1.29 [1.07, 1.55] in Su/Insulin. There were no difference between Diet and Combination therapy groups.
Conclusion
More than half of type 2DM subjects have established CVD in Lithuania. Only minority of them are on statins and most are treated with SU or insulin, which significantly increases the risk of hospitalization for CV events. These results strongly support the need of new antidiabetic medications with proved CV benefit for type 2 diabetes treatment.

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EP190

Matrix–GLA–protein and cardiovascular parameters: uc–dp MGP vs total MGP

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Matrix–GLA–protein (MGP), independent of its posttranslational modification(s), has been associated with bone parameters and cardiovascular risk in patients with and without type 2 diabetes mellitus (T2DM). We investigated whether uncarboxylated, dephosphorylated MGP (uc–dp MGP), total MGP or both are associated with anthropometric and cardiovascular parameters such as carotid to femoral pulse wave velocity (PWV), intima–media thickness (IMT) and relative wall thickness (RWT), in patients with and without T2DM. We analysed data from the BioPersMed cohort ($n=966$, mean age 58±9 years, 255 patients without and 71 with T2DM), a prospective cohort of asymptomatic patients at cardiovascular risk. T2DM and non–T2DM patients were defined according to ADA criteria. Uc–dp MGP was measured using the IDS–iSYS InaKtif MGP Kit and total MGP using Human MGP(Matrix Gla protein) ELISA Kit (Wuhan Fine Biotech Co., Ltd., China). Pulse wave analysis was done with a SphygmoCor device (Atcor Medical, Australia), IMT and echocardiograpy with the Vivid 9 device (GE Healthcare Austria GmbH & Co OG, Austria). Total and uc–dp MGP did not correlate with each other in both subject groups. Uc–dp MGP was associated with BMI ($P<0.001$), weight ($P=0.003$), systolic and diastolic blood pressure ($P=0.021$ and 0.004, respectively), heart frequency ($P=0.011$) and waist and hip circumferences (both $P=0.001$) in patients without T2DM and with BMI ($P=0.016$), weight ($P=0.021$) and waist and hip circumferences ($P=0.025$ and 0.046) in T2DM patients. Total MGP showed no correlations with these parameters in both patient groups. Only uc–dp MGP correlated with PWV, IMT in +patients without T2DM ($P=0.004$ and $P=0.001$, respectively). Those patients with end organ damage had elevated uc–dp MGP levels compared to patients with non–pathologic IMT ($P=0.021$). Only uc–dp MGP showed associations with RWT groups ($P=0.039$) in non–diabetic patients. Patients with eccentric cardiac hypertrophy had higher uc–dp MGP levels than patients with concentric hypertrophy. Uc–dp MGP but not total MGP was associated with cardiovascular parameters in non–diabetic patients and seems to be elevated in pathologic conditions. These findings were not seen in patients with T2DM. Our data implicate that uc–dp MGP is also an active form of MGP and not only an inactive storage form and might be a very interesting player modulating cardiovascular risk.

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EP191

The serological prevalence of celiac disease (cd) in patients with type 1 diabetes (dt1)

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Introduction
Celiac disease is an autoimmune disease triggered by gluten frequently associated with other autoimmune diseases, among which is type 1 diabetes first.
Objectives
The objectives of our study are:
– To determine the serological prevalence of celiac disease (CD) in patients with type 1 diabetes (DT1)
– Compare the clinical and biological characteristics of seropositive and seronegative patients.
Methods
This is as multicenter, cross–sectional study that was carried out over a period of two years. We investigated an adult and pediatric Moroccan population comprised of 276 diabetic type 1 patients, including 144 female and 132 male (sex ratio 1: 1, mean age 14.1±8 years). The screening of CD consisted of the dosage of IgA anti–tTG antibodies, IgA–tTGA seronegative patients with IgA deficiency have been screened for IgG anti–tTG antibodies. HLA–DQ2 / DQ8 typing was performed in patients with low serum anti–tTG and EMA titers.
Results
Among the 276 participants in the study, 25 patients were found to be seropositive, making the serological prevalence 9.1%. Of whom, one patient was found to be IgA deficient and seropositive only to the IgG isotype of the anti–tTG antibodies. 5 patients were advised to perform an HLA determination as they had low titers of both tTG and EMA antibodies, 3 of whom were positive for HLA–DQ2 and 1 for HLA–DQ8. 1 patient was lost to follow up.
Conclusion
Mass screening is to be recommended. However, controlled longitudinal studies with larger samples are needed to prove any potential benefit of a gluten–free diet in similar settings, especially in asymptomatic patients.

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EP192

Autoimmune hypoglycemia: Hirata disease

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Introduction
One of the autoimmune non–diabetic hypoglycemia (NDH) causes is the formation of antibodies to insulin (AB–IRI) or Hirata disease (HD).
Objectives
To determine the prevalence of AB–IRI level increasing in patients with suspected NDH of various genesis and in healthy individuals.
Methods
96 patients aged 18–80 years with suspected NDH were included in prospective study. In all patients we determined the AB–IRI (reference 0–10 U/ml) and IRI levels at the beginning of fasting test (maximally 72h) and controlled glycemia by continuous monitoring system (CMS). According to the results, patients were divided into 4 groups: with insulinoma (group 1), with hypoinsulinemic hypoglycemia (group 2), without hypoglycemia (group 3), with HD (group 4). Also, 10 healthy individuals without hypoglycemia were included and united with patients of group 3.
Results
In group 2 the AB–IRI increasing was not revealed.
HD was revealed in 3.8% of participants (group 4), in whom we noted significantly higher levels of AB–IRI (Me 120.06 U/ml [min 61.1; max 163.55]) and IRI (Me 874.8 μU/ml [min 330.7; max 1000]) compared to other groups ($P<0.000018$). In all patients of group 4 hematological pathology was excluded, the trigger substance was identified (thioctic acid, lisinopril) and canceled. The duration of fast consisted 72h in all patients, but according to CMS the asymptomatic decrease of glycemia (2.4–3.1 mmol/l) recorded in the late postprandial period.
Increasing of AB–IRI, not reaching diagnostic values of HD (AB–IRI carriage), was detected in 2 patients of group 1 (12.81 and 15.64 U/ml) and in 3 participants of group 3 (10.1, 10.14 and 29.7 U/ml) – 4.7% of cases. After surgical treatment of insulinomas (in 2.5 months) AB–IRI remained at the same level ($P=0.94$) in all patients, as in participants №1 and №2 of group

3 when controlled the dynamics in 3 months ($P=0.87$). In participant №3 of group 3 the AB–IRI level in dynamics was normal. There were no violations of carbohydrate metabolism. We continue the patients' observation.
Conclusion
HD is not so rare disease, as seemed previously, accompanied by hypoglycemia (in most cases asymptomatic) in the late postprandial period. The IRI level more than 100 μU/ml testifies in favor of HD, and the diagnosis is confirmed when the AB–IRI level increases, and the fast test is inexpedient. AB–IRI carriage may not cause a violation of carbohydrate metabolism, however, these patients require dynamic observation.
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EP193

Revision of the type of diabetes mellitus– when and why
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Distinguishing type 1 from type 2 diabetes mellitus (DM) depends on clinical presentation, titers of antibodies and requirement for insulin therapy. Need for insulin per se is not a major difference between those two types. We measured the presence of antibodies for glutamic acid decarboxylase (GAD), islet–cell antibodies (ICA), insulinoma–associated protein 2 (IA–2) and the level of C–peptide in a group of 10 patients whose diagnosis of type 2 DM was established several years ago. The reasons for revision were glucose variability, elevated HbA1c in some patients, basal–bolus sheme from the beginning of diagnosis in several patients, presence of unknown hypoglycemias and need for flash glucose monitoring (FGM, "Libre") which is indicated with reimbursement of health care system in type 1 patients in our country. After revision, one male and one female patient were still type 2 DM (ICA, GAD, IA–2 negative, C–peptide 0.35 and 0.41 nmol/l), the duration of disease was 5 and 7 years, respectively. After peroral therapy for 4 and 6 yrs, basal oral regime was used. Among other 8 patients 6 patients were revised to be LADA (two males, 4 females) with positive ICA and GAD, low C–peptide. One male and one female were type 1 (DM 11 and 17 yrs, basal bolus therapy). In 2 pts with LADA, basal–bolus was started from the beginning of diagnosis (duration of DM 6–15 yrs), in 4 pts with LADA duration of DM was 5–30 yrs (peroral therapy first several years). All LADA/ type 1 patients got FGM. Conclusion: availability of FGM and new drugs for DM require that we consider revising the type of DM in some patients in order to provide them with the best care possible.
Keywords: type 1, type 2, revision, flash glucose monitoring.
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EP194

Evolution of the lipidic parameters in a population of elderly subjects with type 2 diabetes who have fasted the month of ramadan
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Introduction
After the fast of the month of Ramadan, the lipid balance of the elderly patients with diabetes can be modified. The aim of our study was to describe the evolution of the parameters of the lipid balance after the fast of Ramadan in a population of elderly diabetic subjects.
Patients and methods: This is a prospective evaluative study conducted in a population of 20 patients with type 2 diabetes aged over 65 years. This population had benefited from an evaluation of the clinical and metabolic parameters before and after the fast and had received education and therapeutic adjustment by referring to the recommendations of the ADA 2016.
Results
The mean age was 68.2±2.4 years with extremes of 65 and 74 years. The sex ratio was 1. The average duration of diabetes was 7.7±6.2 years. The average BMI was 29.5±5.2 kg/m^2 with extremes of 23.18 and 39.87 kg/m^2. 75% were overweight or obese. 90% ($n=18$) were classified as high or very high risk related to fasting according to the classification of the ADA 2016. The days fasted were successive with an average of 26±8.7 days. The majority (80%, $n=16$) had fasted the whole month. After fasting, HbA1C increased from 8.27±1.82% to 8.29±2.1% after fasting (+0.02±1.73%, $P=0.957$) . CT, TG, HDL and LDL were 4.29±0.67, 1.43±0.68, 1.05±0.21 mmol/l, and 1±0.24 g/l respectively, before fasting. They increased respectively after fasting to 4.37±0.68 (+0.08±0.49 mmol /l, $P=0.478$), 1.46±0.46 (+ 0.03±0.43 mmol/l, $P=0.754$), 1.02±0.25 mmol / (–0.03±0.17 mmol /l, $P=0.475$) and at 1.03±0.26 g/l (+0.03±0.12 g/l, $P=0.216$). Gender and body size before fasting were not associated with changes in lipid parameters after fasting.
Conclusion
Several studies report an improvement in lipid parameters after the fast of the month of Ramadan, particularly the elderly. However, fasting in diabetics is not recommended due to the increased risk of acute complications.
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EP195

Insulin therapy and weight gain in type 2 diabetes
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Introduction
Insulin therapy (IT) in type 2 diabetes(T2D) is an integral Pharmacologic Approache because of the progressive nature of the disease. Insulin improves glycemic control and reduces the risk of microvascular complications. It's however associated with weight gain as a side effect which promotes insulinoresistance and cardiovascular morbi–mortality.
In this work we evaluated long–term weight gain in insulin–treated patients with T2D.
Materials and methods
It was a retrospective, descriptive and longitudinal study includng T2D patients on IT for at least 10 years and monitored at the National Nutrition Institute of Tunis. Demographic and clinico–biological data were extracted from the medical record at the initiation of IT and 10 years after.
Results
There were 27 women and 17 men with mean age of 47.7 years old . The average duration of diabetes was 10.78±7.5 years The majority of patients (77.3%) had uncontrolled diabetes with a mean glycated hemoglobin of 9.5±2%. Half of our diabetics were under combination of insulin and oral antidiabetic drugs, 25% with metformin and 20.5% with sulfonylureas. Nearly the a third (38.1%) were on a full basal bolus regimen. Obesity was objectived in 50% of the patients at insulin intiation. the mean initial body mass index (BMI) was 30.65 kg / m^2, with an extreme ranging from 20.9 to 41.4 kg/m. After 10 years of follow–up, 79.9% of patients had unbalanced diabetes. The average weight gain was 2.21±0.8 kg. The mean BMI was 31.14 kg / m^2 with a statistically significant difference ($P<0.001$) compared to the time of insulin intiation.
Conclusions
Weight gain remains a classic side effect of insulin therapy. However, it can be limited by increasing physical activity, calorie intake restriction and concomitant metformin administration.
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EP196

Adherence to anti–diabetic treatment during the fast of the month of ramadan in a population of patients with diabetes
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Introduction
Few studies have examined the adherence to anti–diabetic treatment in patients with diabetes during the fast of the month of Ramadan.
The aim of our study was to describe the adherence to antidiabetic treatment in patients with diabetes before and during the fast.

Patients and methods
This is a descriptive and analytical study carried out on 140 diabetics who have fasted the month of Ramadan. The risk stratification was made by referring to the recommendations of the ADA 2016. Adherence to antidiabetic treatment, was judged: good if the patient regularly takes his treatment at regular times, modertate if the patient does not take his treatment at regular times, bad if the patient does not take all of his treatment and omits some medication during the week.
Results
The majority of the population (82.8% (n=116)) had good therapeutic adherence before fasting. 17.1% (n=24) had moderate to bad therapeutic compliance. During fasting, compliance was good in 80% of cases (n=112), and moderate to bad in 20% of cases (n=28). The frequency of moderate to bad adherence was significantly more frequent in the case of high or very high risk associated with fasting (25.2% (n=25)) than in the case of low to moderate risk (7.3% (n=3)) (P=0.011, OR [95% CI]=4.27 [1.2, 15]).
We studied the association of therapeutic adherence during fasting with the following factors: age, gender, level of study, duration of progression of diabetes, therapeutic adherence before fasting.
None of these factors was significantly associated with adherence during the fasting.
Conclusion
Patients at high and very high risk are often determined to fulfill the religious duty of the fast of the month of Ramadan. Our study showed less adherence to anti–diabetic treatment during fasting in them, which increases the risk of complications, including glycemic imbalance. Thus, we propose to assess therapeutic compliance in diabetics systematically before fasting and to integrate it among the factors classifying as high and very high risk.

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EP197

Real world data of Type 2 Diabetes Mellitus (T2DM) obese patients using another GLP1 receptor agonist (GLP1–RA) and switching to Semaglutide in Spain

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Objectives
Semaglutide was approved for the treatment of T2DM patients with a body mass index (BMI) > 30kg/m^2 by the Spanish National Health Service in May 2019. We evaluate clinical outcomes of patients on previous treatment with any another GLP1–RA that switch to Semaglutide.
Material and methods
Retrospective analysis. Sixty–five T2DM patients were included. Demographic data, anthropometric, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose (FG), glycated hemoglobin (HbA1c) and body composition data were collected at baseline and after 6 months of switching. Statistical analysis was performed with STATA 14. Paired T–student test for comparison between baseline and 6 months and logistic regression to evaluate Semaglutide dose (≤0.5 and 1.0 mg/weekly), age, sex, duration of T2DM, BMI and HbA1c at baseline as possible predictors of Semaglutide efficacy to achieve HbA1c <7%.
Results
Of 65 patients switching to semaglutide (4.6% on 0.25 mg/weekly, 66.15% on 0.5 mg/weekly and 23.07% on 1 mg/weekly), 54.68% were males and the median age was 60.66±9.1 years. Mean duration of T2DM was 12.78±8.2 years. Regarding previous GLP1–RA: 43.0%, 38.5%, 16.9% and 1.5% switch from liraglutide, dulaglutide, exenatide and lysixenatide respectively. Seven patients discontinue treatment because of gastrointestinal intolerance and data of 2 patients were missing, including 56 patients in the final analysis. Waist circumference changed in –2.02 cm (CI95% –3.62 to –0.41) and HbA1C in –0.39% (CI95% –0.74 to –0.05) after switching. There were no changes in other analyzed variables (Table). Semaglutide dose 1.0 mg/weekly (OR: 6.69; CI95% 1.14 to 39.24) and baseline HbA1c (OR 0, 37; CI95% 0.16 to 0.83) were independent predictors to achieve HbA1c <7% after switching to Semaglutide.

	Baseline	Change from Baseline		
		0.5 mg n=39	1.0 mg n=15	Total N=56
Weight–(kg)	98.2±14.84	–0.88	–0.62	–0.58 (–1.71 to 0.54)
Waist–(cm)	116.1±9.4	–1.93	–2.33	–2.25 (–3.67 to –0.84)*
SBP–(mmHg)	133.5±14.17	–0.30	+0.77	–0.40 (–5.37 to 4.56)
DBP–(mmHg)	81.37±11.47	–0.66	–3	–1.45 (–3.78 to 0.89)
Fat–(%)	40.9±8.0	+0.25(n=12)	+3.48(n=6)	–0.57 (–5.57 to 4.42)(n=18)
Lean mass–(kg)	33.1±7.3	–1.11(n=12)	–1.55(n=6)	–1.09 (–2.84 to 0.67)(n=18)
BMI–(kg/m^2)	35.4±5.0	–0.26	–0.18	–0.17 (–0.55 to 0.21)
FG–(mg/dl)	157.4±55.1	+8.18	–9.47	+3.93 (–13.10 to 20.97)
HbA1C–(%)	7.6±1.2	–0.18	–0.99 (–1.93 to –0.03)*	–0.34 (–0.66 to –0.01)*
Insulin dose (UI/day)	50.4±33.6	–1.86(n=15)	–3.63(n=8)	–1.67 (–6.14 to 2.81)(n=24)

*P< 0.05. Two patients (semaglutide 0.25 mg/weekly) are not included in the table.
Data in mean±SD, mean(CI95%)

Conclusions
Patients with T2DM and obesity using previously GP1RA and switching to semaglutide 1 mg present better glycemic control and less waist circunference.

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EP198

Relation between type 1 diabetes management and interactive diabetes education

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Background
Type 1 diabetesmellitus (T1DM) isthe most widespread metabolic/endocrine condition among children/adolescents in Georgia. T1DM patients aged 0–18 yrs are treated both in– and outpatiently. In 2015–2019 totally 533 patients were hospitalized, 211 of them had fresh T1DM. Special attention is paid to interactive diabetes education (IDE) of patients/their caregivers, thatis very important for adequate diabetes management. IDE is initiated from the day of admission.
Our aim was to assess the effect of continuous, structured IDE on quality of metabolic control and acute complication incidence in children/adolescentswith T1DM. Goals of IDE are– teaching about signs/symptoms, progression, acute complications (causes, signs/ symptoms, prevention and treatment) of T1DM; developing insulin injecting, self–monitoring/self–controlskills (result interpretation; bread–units; physical activity, etc).
Methods
Patients treated/supervised at our Hospital were separated into 3 groups (Gr.): 211 patients with fresh T1DM (Gr.1); 150 patients with poor (Gr.2) and 361 patients with satisfactory (Gr.3) glycemia control. Following parameters: HbA1c, hyper–/hypoglycemic coma and ketoacidosis incidence, insulin doseswere studied and compared before/after IDE course and psychologist counseling.
Results
Data obtained before IDE for Gr. 1, 2, 3: HbA1c (%) – 13.5±2.1; 12.5±2.3;7.0±2.5, respectively; hyperglycemic coma (%) – 17; 30; 5, respectively; ketoacidosis (%) – 78; 20;0, respectively; hypoglycemic coma (%) –22; 35; 0, respectively; insulin doses (U/kg) – 1.7±0.1; 1.3±0.4;0.7±0.4, respectively; QOL/Relation to Condition Questionnaire/

RCQ (%) scores were 100; 80;35, respectively. Post–education data: HbA1c (%) – 7.0±2.1; 8.0±2.2;6.4±0.8, respectively; hyperglycemic coma (%) – 0; 4;0, respectively; ketoacidosis (%) – 3; 8; 0, respectively; hypoglycemic coma (%) –0; 0;0, respectively; insulin doses (U/kg) – 0.7±0.1; 0.9±0.4; 0.7±0.12, respectively; QOL/RCQ (%) scores – 95; 87;97, respectively.
Conclusion
IDE, initiated at the moment of diagnosis, that lasts throughout in–hospital period, is regularly repeated out–patiently and tailored to individual patient needs gives knowledge, develops skills, creates motivation, helps to achieve good diabetes control, reduces and/or avoids acute complications and improvesQOL of children and adolescents with T1DM. Lately the first book for children, adolescents and their caregivers "Diabetes Mellitus for Children and Adolescent" was published in Georgian, it discusses all aspects of life with diabetes and management of the condition in a simple and attractive way. The book is delivered free of charge.

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EP199

Hypothyroidism and diabetes in syrian refugees

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Treating Syrian refugees with diabetes, hypertension and Hypothyroidism in Azraq refugee camp, Zarqa, Jordan
Background
Arabian Medical Relief under the donation of UNHCR has been providing primary health care for Syrian refugees at Village six in Azraq refugee camp, Zarqa, Jordan, their services include non–communicable diseases(NCDs) management, apart from other health services. The objectives of this study were to describe the method of care and management for this population, assessing treatment outcomes and challenges met at the NCD clinic.
Methods
A descriptive retrospective cohort study using routinely collected data from the medical files for all active patients attending the NCD clinic at village six in Azraq camp primary health center in 2019.
Results
Of 493 Syrian patients with NCD attending the clinic, 232 patients have hypertension, 109 patients have T2DM, 10 patients have T1DM and 47 patients have hypothyroidism, all of them are active patients visiting the clinic at least every three months in 2019. Regarding all NCD patients, they are predominantly females (57%), and mostly diagnosed before reaching the camp (67%) and most patients are from age group (40–59): 43%.
Outcome
66% of T2DM patients had controlled DM (HbA1C<7.5%) 43% of them are either without treatment or on metformin alone, 99% had controlled blood pressure (BP: <140/90 mmHg) 50% of them are either without treatment or on one medication only, 76% patients of hypothyroidism has a controlled disease (TSH: 0.5–2.5) and none of T1DM patients is controlled
Conclusions
The control rate of NCD at the level of Azraq camp is promising, especially for hypertension, using only essential drug list of the UNHCR, T1DM is very difficult to control and should be investigated more.

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EP200

Remogliflozin reduces gout risk in type 2 diabetes

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Background and aim
SGLT2 inhibitors are relatively new class of medications in the management portfolio of type 2 diabetes (T2DM). Despite their late introduction, they have gained substantial up–gradation in the treatment algorithm as suggested by various international bodies. Remogliflozin is an SGLT2i licensed in India and several other countries for the management of T2DM. We studied the effect of Remogliflozin on serum uric acid (SUA) levels in subjects with type 2 diabetes.
Methodology
In this prospective trial subjects visiting a specialized diabetes centre in Eastern India with T2DM, but without any other documented chronic diabetic complication were invited to participate. Once consented, all of them were administered Remogliflozin 100 mg twice daily for 3 months in addition to their existing antidiabetic regimen. Individuals were instructed to maintain their diet unchanged throughout the study period. During the review visit at the end of the third month, 2 subjects were lost to follow up and 1 person discontinued therapy due to hypoglycemia. Data of 44 adults (32/12 Males/Females) were considered for analysis.
Result
The mean age, weight and UA level of the sample were 49.4±8.6 years, 67.28±11.4 kg and 6.5±2.3 mg/dl respectively. After 3 months the cohort showed a significant drop in the UA level and weight (1.05±1.1 mg/dl and 1.99±2.4 kg respectively). When arranged in declining order of SUA reduction, in the upper sries 10 out of 22 subjects (45.4%) had a SUA drop of ≥1 mg/dl, whereas only 31.8% (7 of 22) had similar SUA reduction in the lower series ($P<0.05$). Mean SUA reductions in the upper and lower series were 1.13±1.3 and 0.97±1.0 respectively. Similarly mean weight loss in both the series were2.3±2.1 kg and 1.7±2.1 kg in order. A numerical drop in the level of SUA was noted in majority (95.5%) of the individuals. Overweight & obese subjects showed a greater SUA reduction when compared to those with normal BMI ($P<0.05$). Out of 16 adults with hyperuricemia (SUA >7 mg/dl), 12 (75%) could achieve normal UA without additional agents.
Conclusion
Remogliflozin reduced serum uric acid significantly, which was more prominent in overweight and obese individuals. This could be helpful while managing patients with type 2 diabetes and hyperurecemia with/ without obesity.

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EP201

Hospitalization cost of diabetic foot ulcerations treated by multidisciplinary team in clinical practice: A restrospective study from Southern Turkey

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Purpose
Diabetic Foot Ulceration (DFU) is common problem throughout the world and resulting in major economic consequences for the patients and country. We aim to describe estimated cost of illness between patients with DFU in southern Turkey.
Methods
A total of 148 ($F=55$, $M=93$) patients with DFU were included in this retrospective study. We also included more than one admission of the patients with DFU. Patients characteristics, duration time of hospitalizations, biochemical parameters, having diabetic retinopathy, nephropathy, neuropathy, coronary artery diasease and peripheral artery disease were recorded from our database. The cost of each patient was recorded from financial affairs and billing department unit of our hospital.
Results
The average unit cost of each patient was £ 733.47±665.32. The major dispenses in the total cost were medication (281.2±412.5) and hospitalisation fee (74.9±54.3). 115 (77.7%) of the patients had periferic arterial diseases. While we could not determined significant correlation between the patients demographical features (age, gender, $P>0.05$), biochemical parameters (plasma glucose, HbA1c%) and diabetes mellitus year (P); lenght of the hospitalization, having periferic artery diseases and performed amputation (minor or major) were significant correlated with total expenses.
Conclusion
The study revealed that the cost of DFU could show a variability in relation with development of countries. We highlighted as similar studies in other countries, major increasing factor of total expenses were lenght of hospitalization, medication and presence of surgery.

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EP202

MicroRNA-107 relation with severe insulin resistance

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It has been shown that miR-107 regulates insulin sensitivity, but its status in severe insulin resistance (IR) patients has not been established. In this study, we investigated the expression of microRNA-107 in the sera from patients with clinically severe IR and its relationships with metabolic characteristics.
Methods
The expression of microRNA-107 was detected in the sera of 30 clinically severe IR patients and 24 gender and age-matched control group by quantitative real-time PCR. Patients that daily insulin requirements were >1 unit/kg/day and HbA1c >9% – referred as clinically severe IR group, patients that daily insulin requirements were <0.9 unit/kg/day and HbA1c <8% – referred as control group. The clinical data were collected and analyzed by statistical software.
Results
In the severe IR group, microRNA-107 level was not higher significantly in the sera (P 0.54).
Conclusions
While microRNA-107 is related with insulin sensitivity, but it is not associated with severe IR.

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EP203

Association of type 1 diabetes with overlap syndrome: A case report

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Introduction: Primary biliary cirrhosis and autoimmune hepatitis are two chronic liver diseases. An overlap of the characteristic signs of these two conditions, determining an 'Overlap syndrome' can be seen. Type 1 diabetes can be associated with this syndrome due to the autoimmune predisposition.
Observation
We report the case of a young type 1 diabetic patient referred to our service for additional management of a glycemic imbalance. This is a 15 year old female patient with type 1 diabetes since the age of 4. The clinical examination showed a diffuse sensitivity of the supra-umbilical stage with a maximum in the right hypochondrium and hepatomegaly. In biology, hepatic cytolysis was found to be 17 times normal and anicteric cholestasis with high γGT (3 times normal) with correct TP. As part of the exploration of this hepatopathy, hepatitis B and C serologies and an autoimmunity assessment were requested. The anti mitochondria and anti smooth muscle antibodies were negative, on the other hand the gp 210 and SLA/LP antibodies were positive. The liver biopsy puncture objectified a chronic liver disease with septal fibrosis classified A2F2 according to Metavir framing with a primary biliary cirrhosis associated with lesions of autoimmune hepatitis (interface hepatitis) evoking an Overlap syndrome. The patient was put on ursodeoxycholic acid, corticosteroid therapy and immunosuppressant. The evolution was marked by the rapid normalization of cholestasis and cytolysis.
Conclusion
Our observation illustrates the importance of early diagnosis of autoimmune diseases that may be associated with type 1 diabetes in order to allow rapid and adequate medical care.

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EP204

Primary prevention of type 2 diabetes mellitus among persons with impaired glucose tolerance in Belarus

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Aims
The aim of our study is to assess the efficacy of lifestyle modification and picolinate chromium intake in preventing diabetes mellitus type 2 (DM 2)
Materials and methods
The study included 100 patients (69 m 258 f) 25–65 years with impaired glucose tolerance (IGT) and newly diagnosed DM 2. Patients were divided into 2 groups matched by age, weight, body mass index (BMI), waist-to-hip ratio (WHR). Research group included 54 patients who carried out recommendations of a balanced diet, physical activity and picolinate chromium was taken 200 mkg per day for 1 month. Control group included 46 patients who did not lifestyle modification. The study was 24 weeks. We measured fasting plasma glycated hemoglobin (HbA1c,%) and related to fasting leptin (FL).
Results
Patients of the research group demonstrated reduction of BMI (–3.2±2.1 kg/m^2) and WHR (–0.02±0.025) (P<0.01 for all) and positive dynamics of HbA1c (P<0.001). Persons of the control group had increase BMI, WHR as also HbA1c elevation (P<0.05). The main novel finding was that median serum leptin in research group decreased on –23.9% (P<0.01) and increased in control group on +27.6% (P<0.01). Among subjects with IGT from the research group, HbA1c normalized in 49.3% (P<0.001) and serum leptin levels decreased on 26.9% (P<0.01). In control group HbA1c normalized in 4.5% (P<0.01). Among patients of the research group was a reduction of DM 2 by 11.9% and an increase in the control group by 35.1%.
Conclusion
Lifestyle modifications with picolinate chromium intake leads to the restoration of glucose homeostasis and preventing DM 2.

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EP205

Influence of the time gap between appointments on type 1 Diabetes Mellitus patients' control

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Introduction
One of the often-discussed topics in the management guidelines for Type 1 Diabetes Mellitus (T1DM) is the ideal time gap that should exist between patient check-ups. A period of three to six months is usually recommended, which sometimes is difficult to achieve due to the high number of patients. But to what extent does the time gap between appointments in the follow-up of T1DM patients affect their diabetes' control?
Objectives
To know the average time gap between T1DM patients' appointments in our hospital; and to quantify the correlation between that time gap and HbA1c, and the correlation between those variables and severe hypoglycemia.
Methods
A retrospective cohort study of 130 T1DM patients who attended to the Endocrinology consults in Hospital Clínico Lozano Blesa, Zaragoza (Spain) was conducted, correlating the time gap between appointments with HbA1c and Clarke score, as well with the presence of severe hypoglycemia. Statistical analysis was performed using Pearson correlation coefficient and Student's T-test.
Results
A positive correlation was observed between the time gap between check-ups and the HbA1c (correlation coefficient 0.357, P<0.01), the HbA1c increase from the previous check-up correlation coefficient 0.564, P<0.01), and Clarke's questionnaire score (correlation coefficient 0.472, P=0.026), as well as between HbA1c and Clarke test score (correlation coefficient 0.387, P=0.04). Moreover, the HbA1c and time-gap mean was significantly higher in those patients who had an episode of severe hypoglycemia (8.05% and 149 days) compared to those who did not (7.32% and 109 days; P=0.017).
Conclusion
Lower HbA1c and Clarke test scores were observed when the time gap between type 1 diabetics' follow-up is shorter, thus achieving better control of their diabetes and having less risk of long-term complications. On the other hand, there is also a higher HbA1c mean in patients who presented severe hypoglycemia, which indicates the importance of time in range and glycemic variability and not only the mean glucose levels estimated by HbA1c.

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EP206

Diabetic ketosis revealing a malignant tumor

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Introduction
Although a strong association between diabetes mellitus and carcinogenesis is suggested, their relationship is still debated. Diabetic ketosis is an acute metabolic complication caused by absolute or relative insulin deficiency. It is rarely a revealing condition of a malignant tumor.
The aim of our study was to determine clinical and paraclinical particularities of patients with malignant tumors revealed by a diabetic ketosis.
Patients and methods
We conducted a retrospective study in patients who were admitted for a diabetic ketosis between 2015 and 2019 and in whom a malignant tumor was revealed. Clinical, biological and radiological features were collected.
Results
Our study included six patients (4 men and 2 women) with an average age of 73.6±15.6 years [Extremes: 48–89]. A family history of hypertension and diabetes was present in three patients. Three patients had type 2 diabetes mellitus. Symptoms were dominated by weight loss, weakness and anorexia in all cases and by epigastralgia in only one. On clinical examination, patients had a mean body weight of 55.3 kg, a mean body mass index of 21.36 kg/m², a mean systolic blood pressure of 106 mmHg and a mean diastolic blood pressure of 66 mmHg. Dehydration was present in one patient and only one patient had a Glasgow score of 12/15. The mean value of capillary glycemia was 4.10 g/l and all patients had ketonuria. The mean level of HbA1c was 11% [extremes: 9–14.8%]. Renal and hepatic functions were normal. Obvious precipitating factors were not present. Tumor markers CA-19–9 were elevated in one case and CA-125 in another case. Investigations revealed pancreatic carcinoma (2 cases), kidney carcinoma (1 case), hepatic carcinoma (1 case) stomach carcinoma (1 case) and brain carcinoma (1 case). Three patients had metastases.
Conclusion
Diabetes mellitus and cancer are common diseases. Their coexistence is possible and may be explained by several factors. This case series study highlights the possibility of coexisting cancer as a ketosis precipitating factor in type 2 diabetic patients and in undiagnosed diabetic patients especially in elderly with a poor general condition and in the absence of obvious precipitating factors.

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EP207

Ketosis-prone diabetes: An emerging worldwide clinically important entity

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Introduction
Ketosis-prone diabetes or Flatbush diabetes has been recognized as a clinical entity since 1984. Is characterized by diabetic ketosis or ketoacidosis occurring soon after the onset of hyperglycemic syntoms (usually poyiuria, polydipsia and weight loss are present for less than 4 weeks). Unlike the insulin dependence seen in type 1 diabetes, after a few weeks (usually 2 to 12 weeks), insulin requeriments decrease, and approximately 70% of patients achieve remission and can be managed by diet alone. Most patients are overweight or obese and is reported in African-American or western Sub-Sahara-African, Hispanic descendant, and recently in Asian.
Case report
A 24-year-old male of Assian origin was admitted to our hospital in January 2014. He presented polyuria, general fatigue and a 6 kg weight loss in the preceding three weeks. Hyperglycemia had never been detected on regular check-ups.
In the emergency room his serum glucose was 323 mg/dl. Arterial blood gas analysis showeed pH 7.22, bicarbonate 19 mEq/l and ketoneuria>80 mg/dl. Islet-related autoantibodies, such us those against GAD, IA-2 and anti beta cell were all negative. On admission his body mass index was 28.29 kg/m². He received intensive insulin therapy and fluids infusion, and during the remainder of hospitalization his insulin requirement was approximately 1.5 U per kilogram of body weight per day. After discharge his treatment was adjusted form intensive insulin subcutaneous injection to only basal insulin and after 3 months to oral hypoglycemic drugs, and finally, after 20 weeks, he was managed with diet alone. He achieved and manteined remission during this 5 years.
In the last visit his plasma glucose was 112 mg/dl and HbA1c 5.4% with diet alone.
Conclusion
When an overweight or obese young patient debut with diabetes mellitus with negative auto-antibodies and diabetic ketoacidosis, with partially preserved beta cell functional reserve after the acute of diabetic ketosis we must thing in KPDM as a posibility.

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EP208

Lateral thinking in new onset diabetes

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A 54-year-old gentleman presented to his GP in July 2019 with significant weight loss, polyuria and nocturia for two to three months. His HbA1c was 78 mmol/mol. He was diagnosed with diabetes and started on Metformin 500 mg BD. Upon consultant review in September 2019, he reported a 26 kg weight loss over the preceding four years, much of which was apparently intentional, and right abdominal discomfort. His paternal grandmother died of pancreatic cancer, as did his paternal aunt. His maternal grandfather had diabetes and maternal grandmother had rheumatoid arthritis. He smoked 20 cigarettes per day for thirty years and drank alcohol in moderation. His systemic examination was unremarkable. There was no significant skin rash and urine ketones were negative. Full blood count, liver function tests and electrolytes were within normal limits. The possibility of type 1 diabetes was considered in view of his initial presentation, but, GAD and IA2 antibodies were negative. Given the weight loss and family history, CA 19–9 and MRI pancreas were requested. The CA 19–9 was normal and MRI pancreas and subsequent CT chest, abdomen and pelvis revealed a 5 cm pancreatic body tumour and multiple bi-lobar liver metastases. One of the hepatic lesions was biopsied and histology reported a well differentiated neuroendocrine tumour, with Ki67 highlights up to 5% of tumour nuclei. Immunohistochemistry revealed strong positivity with cytokeratin, synaptophysin and CD56. CK7, CK20 and chromogranin were negative. Octreotide scan demonstrated avidity in the pancreatic body primarily and bi-lobar liver metastases. There was no uptake in other areas. Ga68 DOTATATE PET confirmed the diagnosis by showing high uptake in body of pancreas and liver metastases (somatostatin 2 receptor positive). His PTH and calcium level were normal, likely excluding MEN1. His fasting glucagon level was 73 pmol/l (0–50) and chromogranin A was 151 pmol/l (0–60). Chromogranin B was>250 pmol/l (0–150). Vasoactive intestinal peptide, pancreatic polypeptide, gastrin and somatostatin were normal. Somatostatin analogues were initiated as first-line therapy.
In conclusion, this case highlights the importance of careful consideration of the differential diagnosis when patients present with new-onset diabetes and atypical features, and awareness of neuroendocrine tumours (NET) of the pancreas as a cause.

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EP209

Diabetic nephropathy and cardiovascular risk

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Introduction
Diabetes is the leading cause of end-stage renal disease in Europe (12 to 30%). In the United States, it is the cause of more than half of the cases of this disease. Renal disease is a cardiovascular morbidity and mortality preacher which is three times more common in diabetic patients with diabetic nephropathy (DN). The aim of our study was to describe the factors of cardiovascular risk associated with ND in a group of type 2 diabetes (T2D) Tunisians.

Materials and methods
It was a transversale, retrospective and descriptive study including 75 T2D patients with a confirmed ND, collected in the Diabetology departments of the National Institute of Nutrition and Food Technology of Tunis between 2018 and 2019.
Results
There were 42 women and 33 men with mean age was 62.25±9.3 years. The body mass index was 29.67±5.43 kg/m². The average duration of diabetes was 9.48±6.88 years. In 90.6% of cases, treatment was insulin therapy. ND was at the microalbuminuria stage in 60 patients and 46.6% had renal failure (GFR <90 ml/min). High blood pressure was present in 44 patients, 81% of whom were on ACE inhibitors. Other microangiopathic complications were present, such as diabetic retinopathy in 28 patients, 6 of which had a proliferative form and peripheral neuropathy in 38 patients. Coronary artery disease was found in 9 patients and arteritis of the lower limbs in 9 patients also when two had suffered a stroke. Hyper triglyceridemia was observed in 27 patients, hypo-HDL-cholesterolemia in 35 patients and hyper LDL-emie in 65 patients. We did not found a correlation between the micro and macro albuminuria of a part and the presence of a coronary disease of another part (P=NS). We noted a positive correlation between the ND stage and the glycemic balance (P=0.04). However, no correlation has been demonstrated between the micro and macro albuminuria firestly and the triglyceride level (P=NS), HDL cholesterol (P=NS) and the LDL cholesterol level (P=NS) on the other hand.
Conclusions
Kidney damage increases the cardiovascular risk in T2D. Its prevention and management requires an optimal glycemic and blood pressure balance in order to protect not only the kidney but also the heart and thus improve the prognosis of diabetics.

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EP210

Anemia in diabetic patients

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Background
Anemia is a common finding in patients with diabetes mellitus which increases the progress of the diabetic complications. There are several factors which cause anemia out of renal failure in diabetics. In this study, we aimed to investigate the frequency of anemia and factors that decreases hgb levels in diabetic patients
Methods
This retrospective study includes 207 diabetic patients that were hospitalized between january 2019 and january 2020 at Eskişehir Osmangazi University Hospital, Endocrinology department. Patient's data included demographics, complicationts, medications and labaroutary results. Anemia was defined as hemoglobin (Hgb) concentrations < 13 g/dl in men and < 12 g/dl in women
Results
Of 207 hospitalized patients with diabetes 42% had anemia. Diabetic males had a higher rate of anemia compared to females (54.7% vs 34.8% respectively, P<0.008) Diabetic patients with a history of diabetic foot ulcer were more likely to be anemia. However there was no relationship between albuminuria and anemi frequency in diabetics without renal failure.
Conclusion
In this study we've found a positive correlation between diabetic foot ulcer and anemia. On the other hand there was no significant difference between macrovascular and microvascular complications with anemia. Patients with a history of diabetic foot ulcer should be considered anemia predictor and treated earlier.

Table 1

	Anemic	Non-anemic
Male(%)	45.3	54.7
Female(%)	34.8	65.2
Vitamin B12 defficiency(%)	22.1	11.2
DRP(%)	47.1	33
Diabetic foot (%)	18.1	5.8
Nöropati(%)	32.9	27.2
Metformin(%)	40.2	42.9

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EP211

Charcot foot: Early diagnosis and interest in medical care: A case report

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Introduction
Charcot foot is a painless progressive osteoarthropathy of one or more joints due to an underlying neurological lesion, leading to deformities of the foot by the non-infectious destruction of bones and joints.
The interest of this observation is to show on the one hand the role that the education of diabetics plays in the early diagnosis of Charcot foot and on the other hand the need for a multidisciplinary team in the care of the foot of Charcot.
Observation
This is a 35 year old patient with type 1 diabetes, uncomplicated, from the age of 21 who presented to our emergency room for left foot edema evolving for two weeks. The clinical examination showed an edematous, hot, red and painless left foot. There is the absence of a wound or infection and the absence of general signs. The standard x-ray of the left foot was normal. Within the framework of the exploration of this localized edema, an MRI was requested objectifying an aspect related to a diabetic osteoarthropathy rather than an infectious osteoarthritis with involvement of the bone marrow of the metatarsals of the 2nd, 3rd and 5th rays as well as joint damage involving the metatarsophalangeal muscles of the 2nd and 5th rays without visible fracture or subperiosteal abscess.
The patient was referred to the physical medicine department for additional treatment, where he was provided with suitable shoes with a foot orthotic relief orthosis.
Conclusion
Our observation illustrates the value of early diagnosis of complications that may be associated with type 1 diabetes in order to allow rapid and effective management which will preserve the patient's functional or even vital prognosis.

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EP212

The bidirectional link between diabetes mellitus and oral health: A study in Albanian patients with diabetes

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Background and aims
Diabetes mellitus (DM) is a chronic, metabolic disease that is spreading rapidly around the world. Various studies have shown the association between DM and oral health. The aim of this study was to evaluate the knowledge patients with diabetes have regarding the impact of diabetes mellitus on oral health; the role of oral hygiene care and dentists follow up.
Methodology and methods
The survey research was taken in 79 Albanian patients with diabetes, hospitalized in the Endocrinology Service. A multiple-choice questionnaire was used to assess their knowledge and their habits regarding diabetes and oral health.
Results
Participants were aged from 20 to 81(mean 59.88) years old; 44(55.7%) females and 35 (44.3%) males; elementary, middle school and high education, 34 (43%), 34(43%), 11(14%) respectively. From the results of the questionnaire the following data were observed: 35 patients (44.2%) didn't know the direct link between DM and oral health; 65 patients (83.3%), females 41 (63%) and males 24 (37%), where 11 patients (100%) with high education, 32 (94.11%) patients with middle education and 22 patients (64.7%) with elementary education, knew the importance of oral hygiene in oral health. A

low number of patients 19 (24.4%) visited the dentist regularly. There was no change between ages.
Conclusions
According to the data analysis, the awareness of the link between DM and oral health, in the Albanian patients with diabetes should be improved, particularly in the patients with lower education. Incidence and severity of oral diseases in patients with diabetes can be reduced by regularly visiting dentist.

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EP213

Comparative risk factors of diabetic foot complications for type 1 and type 2 diabetes mellitus

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Objective
Diabetic foot complications are a main cause for hospital admissions and spending for patients suffering from T1DM or T2DM. The purpose of this study was to identify and compare possible risk factors for patients suffering from such issues.
Methods
We conducted a retrospective observational study analyzing data from observation charts of 324 patients, diagnosed with T1DM or T2DM as well as various foot issues, evaluated between January 2015 – December 2017 in our clinic. The patients were divided into 2 groups: T1DM and T2DM (40 and 284 patients – 25% female and 75% male, respectively 23% and 77%).
Results
The T1DM group was younger ($P=0.0000012642$), leaner ($P=0.0000000043$), had been diagnosed at a younger age ($P=0.00...01$), had a longer duration of disease ($P=0.0000200919$), more hospital admissions (1.97 vs 1.41, $P=0.015709446$), poorer glycemic control (9.69 vs 8.60%, $P=0.000124519$), but better TG and HDL-cholesterol levels (137.20 vs 165.99 and 47.65 vs 39.82 mg/dl, $P=0.030880937$, $P=0.003798103$). Statistically significant differences between patients with amputations and those only with soft tissue damage for the T2DM group: sex ($P=0.022714$), kidney impairment ($P=0.01$ 989), retinopathy ($P=0.01$ 0754), mean no. of days/hospital admission (8.06 vs 7.26 days, $P=0.029889513$), BMI (29.35 vs 30.64 kg/m^2, $P=0.04805204$), glycemic control (8.38 vs 8.86%, $P=0.040931604$), HDL-cholesterol levels (38.73 vs 41.05 mg/dl, $P=0.04$ 601). For the T1DM group: kidney impairment ($P=0.003782032$), mean no. of days/hospital admission (9.06 vs 6.12 days, $P=0.0000191641$), total and LDL – cholesterol (161.19 vs 188.15 and 88.25 vs 109.35 mg/dl, $P=0.019094005$, $P=0.013594543$).
Conclusions
Identifying risk factors should help in establishing prevention measures for diabetic foot issues.

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EP214

Clinical and biological characteristics of non-reactive hypoglycemia in non-diabetic adults

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Introduction
Hypoglycemia is common in diabetic patients as an adverse effect of their medication. A minority of hypoglycemia occurs in non-diabetic patients. This spontaneous hypoglycemia defined by the Whipple's triad results from organic (non-reactive) or functional (reactive) causes, and in few cases, a factitious hypoglycemia, posing an etiological problem. The aim of our study was to assess clinical and biological features of non-reactive hypoglycemia in non-diabetic adults.
Methods
This is a descriptive, retrospective and single-center study including 65 patients with a confirmed hypoglycemia according to the presence of Whipple's triad. Patients without a precise cause of hypoglycemia, patients with factitious hypoglycemia and those with iatrogenic causes were excluded. Clinical and paraclinical features were collected and compared between patients with non-reactive hypoglycemia (group 1) and those with reactive hypoglycemia (group 2).
Results
The study population included 40 patients with a sex-ratio of 1.6 and a mean age of 45.3±16.6 years. The diagnosis of non-reactive hypoglycemia (adrenal insufficiency $n=22$, insulinoma $n=4$) was established in 26 cases (65%) and reactive hypoglycemia in 14 cases (35%). There was no significant difference between the two groups according to the age (group1: 45.9±18.3 years, group2: 44.1±13.4 years, $P=0.8$). A female predominance was found in group 1 (73% vs 43% in group 2, OR=3.6, $P=0.06$). Fasting hypoglycemia was more frequent in group 1 (66%) than in group 2 (7%) (OR=20.8, $P=0.001$). The prevalence of neuroglycopenic symptoms was 81% in group 1 vs 64% in group 2 ($P=0.22$). Group 1 had a lower body weight (65.1±16.2 kg vs 75.2±12.0 kg in group2, $P=0.03$) a lower systolic blood pressure (11.1±1.7 cmHg vs 12.2±1.6 cmHg, $P=0.05$) and diastolic blood pressure (6.9±0.9 vs 7.7±0.9, $P=0.03$). The prevalence of overweight was 48% in group 1 vs 52%, in group 2 ($P=0.06$). A blood glucose level<0.3 was found in 23% in group 1 vs 0% in group 2, ($P=0.06$)
Conclusion
Non-reactive hypoglycemia was predominant comparing to reactive causes, with a female predominance, related to the higher prevalence of adrenal insufficiency in women. The predictive factors of organicity were fasting hypoglycemia, blood glucose level<0.3, lower body weight and lower blood pressure. Fasting hypoglycemia is the most predictive and should guide etiologic investigations toward organic causes.

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EP215

Decalogue of venipucture process of an experienced nurse in adult patients with prader willi syndrome

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Background
Prader-Willi syndrome (PWS) is a genetic neurodevelopmental disorder characterized by marked hyperphagia and morbid obesity, together with hormone deficiencies, abnormal behaviour in relation to food (obsessive thinking, food foraging, stealing, etc.). Veins in patients with PWS are difficult to find due to obesity and probably to generalised hypotonia including venous tone. Since treating a patient with PWS often requires the acquisition of blood samples, an experienced nurse is mandatory in the multidisciplinary team.
Objective
On the basis of our experience, we propose some recommendations to be taken into account for blood sample collection in adult patients with PWS.
Methods
Recommendations based on grade E of evidence
Results
The following items must be taken into account: Drink a lot of water the night before, come to hospital with clothes with warm long sleeves, use local heat with hot gel, gain her/his confidence, make her/him to be comfortable, use gloves and double tourniquet 5–10 cm above venepuncture site, use alcohol pads in order to dilate the veins, use butterfly, have all the tubes to be filled near in order of priority, just in case you cannot get enough blood for all. If blood does not come out, put the arm below heart level or raise the forearm o turn the wrist so as to get more circulating blood. If you cannot get a good vein, then proceed to artery puncture (radial). Remember that they do not feel pain (high threshold) or if the patient is afraid of feeling pain, use lidocaine cream. Put an adhesive pressure strip. Use biohazard waste container. Finally, do not forget to draw and keep a map of good veins for every patient so as to check next time she/he comes.
Conclusions
Following a nurse protocol for blood collection and other care issues in adult patients with PWS is essential for the best achievement of clinical assays, investigational projects and also the routine clinical care

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EP216

Relationship between high serum uric acid and postoperative central diabetes insipidus for pituitary adenoma patients

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Context
Postoperative central diabetes insipidus (PDI) is one of the most common complications of surgical treatment of pituitary adenoma, temporary or permanant. The diagnosis of PDI was suspicious in some occasions and inappropriate prescription of antidiuretic hormone was harmful. Generally, high level serum uric acid (HUA) was a clue for central diabetes insipidus, but we did not know its role for the brain postoperative subjects. As we know, the food intake and health condition was unstable during the acute short period after operation.
Objective
To explore whether HUA could be an indicator of PDI for those hospilized patients shortly after surgery of pituitary adenoma.
Design and patients
A total of 125 patients received resection of pituitary adenoma with pathologically diagnosed pituitary adenoma in the First Affiliated Hospital of Sun Yat-sen University from November 2017 to June 2019. A retrospective analysis of case records was done. General demographic information, daily lifestyle, anthropometric data and laboratory tests results were collected from case records. Excluding subjects without postoperative serum uric acid measurement, 43 individuals were included in the final analyses. HUA was defined as postoperative uric acid>297.5 μmol/L (5 mg/dl). PDI was defined as postoperative urine volume>4000 ml/24 h or being administrated of desmopressin such as Minirin post operation and prior to discharge. The relationship between PDI and HUA in these patients was analysed with Logistic regression analysis.
Results
The incidence of PDI in this study was 65.1%. The incidence of PDI in patients with postoperative HUA is 75.9% while it was 42.9% in patients without HUA ($P=0.046$). Logistic regression analysis result showed that PDI was a significant factor for HUA. After adjusting for gender, age, the history of hypertension, diabetes mellitus, smoking and drinking, patients with PDI had increased risk of HUA (Odds Ratio (OR)=12.13, 95% Confidence interval (CI): 1.03–142.29) ($P=0.047$).
Conclusion
PDI was a very commom complication of the pituitary adenoma surgery. PDI was associated with HUA in the patients shortly after pituitary adenoma surgery.. Postoperative HUA might be an indicator of central diabetes insipidus in these patients. The limitation here was PDI might contain other reasons of polyurea, such as excessive fluid infusion. Further well designed prospective studies are needed.

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EP217

Characteristics of new diagnoses type 1 diabetes between 2015–2018

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Introduction and objectives
Type 1 diabetes mellitus (T1DM) is a chronic disease with potential consequences for patients, relatives and ultimately for the healthcare system. The objective of this study is to report the incidence of DM1 in our area as well as assess the characteristics of the patients at the time of diagnosis.
Material and methods
Retrospective descriptive study. Data was collected through the registration of new diagnoses of T1DM in a third level hospital during 4 years. Medical records at patient's disease onset were reviewed. In total, data was assessed from 99 patients, including paediatric patients and adults.
Results

New diagnoses	Total:99 • 2015:22 • 2016:26 • 2017:28 • 2018:23
Women/Men	46/53
Age	Mean:28;Median:23 • 0–5 y:9% • 6–10 y:16% • 11–15 y:13% • 16–20 y:7% • 21–25 y:9% • 26–30 y:3% • 31–35 y:8% • 36–40 y:5% • 41–45 y:5% • 46–50 y:6% • 51–55 y:6% • 56–60 y:3% • 61–65 y:5% • 66–70 y:4%
BMI (only in>20 years old)	Mean:24.4%
Symptoms	Diabetic ketoacidosis:17% Cardinal signs:68%;Median of duration:4 weeks.
Age-Ketoacidosis	• 0–5 y:5;55.5% • 6–10 y:5;31% • 11–15 y:3;23% • 16–20 y:2;29% • 36–40 y:1;20% • 61–65 y:1;20%
Laboratory analysis	Glycemia(mean):377 mg/dl Glycated haemoglobin(mean):10.8% C-peptide:0.97;Decreased:68.5%
Previous use of non-insulin antidiabetics	18
Autoantibodies	Included Zinc(*n*:63): • GAD+,IA2 +,Zn +:25;39.7% • GAD+,IA2–,Zn +:12;19% • GAD+,IA2 +,Zn–:7;11.1% • GAD–,IA2 +,Zn +:5;7.9% • GAD+,IA2–,Zn–:5;7.9% • GAD–,IA2–,Zn +:4;6.3% • GAD–,IA2 +,Zn–:3;4.8% • GAD–,IA2-,Zn–:2;3.2% No included Zinc(*n*:36): • GAD +,IA2–:16;44.4% • GAD +,IA2 +:13;36.1% • GAD–,IA2–:4;11.1% • GAD–,IA2 +:3;8.3%

Autoantibodies-Ketoacidosis	• GAD+,IA2+,Zn+:5;20% • GAD+IA2-,Zn+:3;25% • GAD+,IA2+,Zn–:7;43% • GAD-,IA2 +,Zn +:1;20% • GAD +,IA2-,Zn–:2;40% • GAD–,IA2-,Zn +:0 • GAD–,IA2 +,Zn–:0 • GAD–,IA2-,Zn–:0
Haplotypes	n:53 • DR3-DR4+DQ2-DQ8 +:16;30.2% • DR3+DR4+DQ2+DQ8 +:14;26.4% • DR3+DR4-DQ2+DQ8–:13;24.5% • DR3-DR4-DQ2-DQ8–:9;17% • DR3+DR4+DQ2+DQ8–:1;1.89%
Personal history of autoimmune diseases	No:75
Familiar history of DM	T1DM:26 T2DM:45

Conclusions
T1DM incidence in our area was 7.6/100.000 patients. There were no major changes in the incidence in the different years evaluated. Most newly diagnoses were performed before the age of 25, with a higher incidence between 6 and 10 years old. Less than 20% of patients debuted with ketoacidosis. Children are at greater risk of ketoacidosis at the diagnosis of diabetes. In almost 20% of the T1DM patients, non-insulin antidiabetic drugs were initially used. The most frequently detected autoantibodies were GAD+IA2+Zn and GAD+IA2-. Greater tendency to ketoacidosis with respect to other combinations in GAD+IA2+Zn- and GAD+IA2-Zn-. More than 80% of the patients presented positivity in any of haplotypes. The vast majority of the patients did not reported any history of autoimmune diseases. On the other hand, almost a quarter of the patients had family history of T1DM and almost half of T2DM.

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EP218

Dynamics of indicators of cytolysis, carbonyl stress in patients with type 2 diabetes and non-alcoholic fatty liver disease on glucose-lowering therapies

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Objective
To study the dynamics of cytolysis and carbonyl stress (methylglyoxal (MG)) in patients with type 2 diabetes mellitus (DM2) and non-alcoholic fat disease liver (NAFLD) on the background of various hypoglycemic therapy.
Materials and methods
The study included 48 patients, 53.8±11.14 years, with SD2 and NAFLD and 20 people in the control group. Viral hepatitis was excluded, toxic and drug-induced liver injury. Anthropometric researc included: determination of waist circumference, body weight, height, and index calculation body mass index (BMI). Indicators of cytolysis (ALT, AST) and carbonyl stress were evaluated. Patients were divided into 2 groups: 1) inhibitors sodium-glucose cotransporter type 2+Metformin (MF); 2) preparations sulfonylureas (PSU)+MF.
Results
The BMI was 35.8±8.67 kg/2 on average for the group, from 109.5±16.48 sm, which indicated abdominal type of obesity. In patients with DM2 and NAFLD, a higher concentration of MG was detected, compared with the the control group. the following dynamics of indicators: in the first group (I-NGL-2+MF) before BMI treatment was 35.1±6.66, after 12 months 33.8±6.95, in the second group ((PSM)+MF) 36.48±7.66; 39.26±7.64, respectively, the level of glycated hemoglobin (HbA1c): I-NGLT-2+MF: before treatment 8.18±1.52, after 12 months 7.37±1.76, (PSM)+MF: 8.51±1.58; 8.65±1.14 accordingly, ALT level: I-NGL-2+MF: before treatment 72.95±58.79, after 12 months 29.42±18.27, (PSM)+MF: 39.29±45.89; 36.26±23.97, respectively. After 12 month of treatment, In the first group, there was more pronounced weight loss, HbA1c, ALT, MG, as a product of excessive glycosylation, carbonyl stress index.
Conclusions
Based on the results of the preliminary analysis, we can say that inhibitors sodium-glucose cotransporter type 2+Metformin (MF) are more preferable in comparison with PSU in combination with MF, in these patients.

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EP219

Determination of methylglyoxal level as an indicator glucotoxicity with nafld and diabetes 2-type

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Glycation is due to the ability of glucose to form irreversible chemical compounds with amino groups of lysine and arginine – methylglyoxal (MG).
Material and methods
98 patients with NAFLD and 52 patients with NAFLD were examined. Diabetes 2-type, and 22 healthy volunteers. Age 57.3±5.2 years. BMI 34.85±1.79. The diagnosis was established on the basis of laboratory data and examination results. The level of LPO was determinedby the content of malonic dialdehyde (MDA).
Results
In patients with NAFLD, the content of MG in the blood serum520.75±114.35, in the control-69.02±6.67 nm/l ($P=0.001$). In T2DM patients the MG content was 292.11±16.34 nm/l. Observed correlation of MG and MDA ($r=0.495$).
Conclusions
Patients with NAFLD have a significant increase in MG b serum 7 times compared to the control. MG damage arginine residues of proteins, disrupts the transmission of the insulin signal, inhibits enzymes and plays a key role in the development of insulin resistance and hyperglycemia. Quantitative determination of MG in serum by HPLC method can be used as a prognostic and diagnostic test glucotoxicity.
Keywords: NAFLD, type 2 diabetes, glycosylation, methylglyoxal.
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EP220

Cubulin and Megalin gene polymorphisms in diabetes mellitus

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Background
Diabetes mellitus is the commonest endocrinopathy, Worldwide. Inspite of its commonality, the genetic basis of etiopathogenesis and pathophysiology are ever evolving and enigmatic. Amongst the protean genetic variations, cubulin gene and megalin gene mutations in diabetes are important in dictating genotype—phenotypic correlations and natural clinical course of diabetes. The genetic studies in this area are especially very sparse from Indian sub-continent. In this context, we analysed the prevalence of cubulin (CBN) and megalin (LRP2) gene mutations in diabetes patients visavis controls.
Methods
This is inter-disciplinary case control study conducted by collaboration between a tertiary care endocrinology hospital, biochemistry department of a teaching medical institute and genetics lab. In this prospective study, we employed 4 sets of primers and screened for cubulin; CUBN gene polymorphisms (rs1801222 and rs11254363) and megalin (LRP2) gene polymorphisms (rs3755166 and rs2544390). in subjects with type 2 diabetes mellitus.

Results
The percentages of AA, AG and GG in cases were 12.5, 62.5 and 25 while in controls it was 70, 20 and 10 respectively. The allele frequencies of A and G alleles in patients are 0.44 and 0.56 while in controls were 0.80 and 0.20 correspondingly. The percentages of CC, CT and TT in cases were 47.5, 50 and 2.5 while in controls it was 60, 30 and 10 respectively. The allele frequencies of A and G alleles in patients are 0.73 and 0.27 while in controls were 0.75 and 0.25 correspondingly. The difference was statistically significant for CUBN gene and non-significant for LRP2 gene.
Conclusions
For cubulin gene, the AA genotype along with the A allele showed an odds ratio value of 0.06 and 0.19 respectively. The AG and G allele demonstrated 7.5-fold and 5.5-fold risk. For LRP2 gene, none of the genotypes showed a protective or predisposing role.
Keywords: diabetes, cubulin gene, megalin gene, polymorphism.
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EP221

Association of CAPN10, FTO, PPAR, MTHFR gene polymorphisms and obesity with type 2 diabetes mellitus: A study on the bengalee hindu caste population of west bengal, india

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Background
Type 2 diabetes mellitus (DM) is probably one of the non-communicable diseases with raised levels of glucose in the blood due to insulin efficacy. The aetiology of disease combines both genetic and lifestyle or environmental factors. (GWAS) studies have been identified CAPN10 (SNP-19), FTO (rs-9939609), MTHFR (rs1801133) and PPARG (rs1801282) genetic polymorphism with susceptibility to T2DM. The susceptibility will increase by independent risk of genetic polymorphism, obesity and lifestyle factors as well as combinations of these factors. On this background, the present work tried to understand the association of Calpain10 (CAPN10), FTO, PPAR and MTHFR genetic polymorphisms, fat patterning and physiological variables like blood pressure and effect of lifestyle variables with T2DM in Bengalee Hindu caste population of Eastern India.
Materials and methods
The Present study consisted of 104 clinically diagnosed Type2 diabetes Mellitus Male patients and 176 apparently healthy males denoted as control group from Bengalee Hindu caste population of West Bengal, India. Genomic DNA was isolated from mouthwash using Phenol-Chloroform method with slight modifications. Genotyping for all the SNPs/variants was performed by using standard Polymerase Chain Reaction (PCR) method and PCR- RFLP method. Data has been collected on height, weight, waist and hip circumference following standard techniques. Moreover, Percent Body Fat (PBF) and BMI were obtained by Body Scanner (Omron Karada Scan HBF-375) strictly following the manufacturer manuals. Subsequently, fasting blood glucose was also measured by Accuchek (Active) glucometer. Data on lifestyle variables has been obtained through pretested schedule.
Results
MTHFR (rs1801133) genetic variant were significantly ($P<0.05$) associated with T2DM due to increased CT genotypes among Bengalee Hindu caste group. Apart from genetic risk factor, T2DM patients had ($P<0.05$) higher central obesity (WC, WHR) as well as overall obesity (BMI, PBF) and Systolic blood pressure (SBP) compared with control group. Family history of T2DM, hypertension and family history of hypertension were significantly ($P<0.05$) enhanced the risk of T2DM.
Conclusion
The present study envisaged identification of genetic variants and anthropometric variables pertaining to obesity could be used as screening tool for early prognosis of T2DM among Bengalee Hindu caste population.
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EP222

Urinary disorders revealing a wolfram syndrome: A case report

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Background
Wolfram syndrome (WS) is an autosomal recessive neurodegenerative disorder characterized by Diabetes Insipidus, Diabetes Mellitus (non-autoimmune), Optic Atrophy, and Deafness.
We report the case of a patient sent to the physical and rehabilitation department to manage urinary disorders and for whom the diagnosis of WS was retained.
Case report
A 24-year-old female patient, with history of diabetes mellitus type I from the age of 3 years, deafness, optic atrophy, presented with urinary retention. First Echo graphic and biological investigations showed no alteration of the upper urinary tracts. The urodynamic assessment found a hypo contractile retention bladder. Self-catheterization was indicated. However, the patient complained of polyuria. She was followed up in endocrinology department where diabetes insipidus was explored and the diagnosis of WS was, then, retained. The patient had also a history of and insipidus syndrome and was sent to the endocrinology department. The diagnosis of WS was, then retained. The follow-up at 4 years found an alteration of the upper urinary tract.
Conclusion
WS should be considered a differential diagnosis in patients with diabetes mellitus who present with neurogenic bladder, and it is necessary to perform a hearing test and an ophthalmological examination. The urological risk is major requiring a systematic follow-up of these patients.
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EP223

The relationship between milk and dairy consumption and obesity in children between the ages of 7–10

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Introduction: There is some evidence shows daily consumption of milk/dairy products prevents obesity and many diseases. Even in adulthood, the consumption of adequate milk/dairy products in childhood is protective of obesity. Therefore, balanced consumption of milk/dairy products is thought to prevent obesity or overweight, which is an important health problem nowadays. In our study, we aimed to determine whether there is a relationship between the consumption of milk/dairy products and body mass index(BMI) among students studying at Private School and Public School. Material and Method: Our study was carried out by selecting 300 students, 126 Private School, 176 Public School 7–10 years of age. In the survey, cheese, yogurt, ayran, butter, and milk consumption was grouped separately and demographic and daily food frequency questionnaire (FFQ) was taken from the parents of students. Anthropometric measurements are the most important measures reflect nutritional status. In our study, we used the persantil curves of Turkish children (Neyzi *et al.*) which calculated by genetic variations.
Results
The frequency of those who consume milk and dairy products every day was higher among public school students. While those who consume milk every day (57.3 percent) and the majority of those who consume at least 5–6 times a week (57.1 percent) are children studying in public school, the majority of those who never consume (54.5 percent), and the majority of those who consume 1–2 times a week (57.1 percent) are children studying at the Private School. while 54.5 percent of those who consume no dairy are obese according to BMI standards of Turkey, 70.9 percent of those who consume dairy every day with normal BMI value. When we look at consumption, there is a significant difference between BMI values and dairy consumption. While 63.2 percent of those who consumed dairy products daily have normal BMI values, 55 percent of those who consumed it once a month or not at all are weak and stunted.
Conclusion
In literature, it has been shown that milk and/or dairy products added to the diet have positive effects on children's development and BMI. In our study, it supports these findings and the inclusion of milk and dairy products in the daily diet of children should be encouraged. Also, the fact that more milk consumption was detected among the students studying in the Public School was associated with regular daily milk distribution in these schools.
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EP224

Efficiency of ceylon cinnamon on anthropometric indices in polycystic ovary syndrome

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Introduction
Ceylon cinnamon (CC) has shown its interest in insulin resistance, type2 diabetes and weight loss. In this study, we aimed to evaluate the effects of CC on anthropometric indices in patients with polycystic ovary syndrome (PCOS).
Methods
We performed a prospective interventional study, including 13 patients with PCOS, diagnosed according to the Rotterdam criteria, patients having received neither diet education nor Metformin. At T0 all our patients had, a dietary survey, anthropometric measurements: weight, height, waist seize, and impedance. During the intervention, they received a 500 mg capsule of CC three times a day (designed and prepared for the study), without changing their eating habits and physical activity, diabetic patients were excluded of the study.
Results
After 8 weeks (T1), we found a reduction in the mean of the waist seize (delta=–3.4±4.74 cm et $P=0.02$), a significant reduction in the waist size/height Ratio (delta=–0.22±0.03 et $P=0.02$), a non-significant reduction in the average BMI (delta=–0.32±1.34 kg/m^2) and an insignificant reduction in all components of body mass with a maximum for the fat mass at the level of the trunk (delta=–1.3±10.89 kg).
Conclusion
These results could be explained by the anti-obesogenic effect of CC and lead us to suggest it as an etiopathogenic treatment for PCOS.

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EP225

Long term impact of bariatric surgery in severely obese patients in a district general hospital

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Introduction
The efficacy and safety of bariatric surgery (BS) are well documented, but data in our region is lacking.
Aim
Analyze the long term effect of BS on obese patients in a single district hospital. Primary outcomes: –weight change 5–10 years post BS; –patient satisfaction. Secondary outcomes: weight reduction according to type of surgical procedure, sex, public/private hospital; mortality, complications.
Materials and methods
Retrospective data collection from electronic patients record and telephone calls to patients. Study group: all patients undergoing BS before 2015. Control group: 40 obesity patients not treated with BS. Weight data collected for 5–10 years expressed as median of all available weights for each year post-op/post-entry.
Results
58 BS patients (61 procedures); 40 patients not operated. Gastric bypass (GB) 44 procedures, vertical banded gastroplasty (VBG) 7, sleeve gastrectomy (SG) 7, Scopinaro 2, adjustable gastric banding (AGB) 1. Re-operations: 3 VBG to GB, 1 SG to GB. 1 AGB removed year 2 (technical malfunction). Public procedures 88% (Hospital Universitario Donostia), Private 11% (elsewhere).
Long term weight change
Median weight 5 and 10 years post BS: 70% and 74% of pre-OP weight. Control group (no BS): 98% and 103% of initial weight. 68% of BS achieved 20% weight loss at 10 years; 39% achieved 30%. None of control group patients did. Failed operations (defined as 10-year weight loss <5%): 1 VBG patient (3%).
Patient satisfaction
Defined as not regretting having undergone BS. Data collection 67%. 37 patients (94%) did not regret their decision. 1 patient unsatisfied due to refractory hypoglycemia; 1 patient unsure. Weight change according to type of procedure, sex, public/private hospital No major differences apparent (graphs on poster).
Mortality
One death identified: over 10 years after BS, cause of death considered unrelated.
Complications
Defined as any hospital admission within 2 years of BS.
Data collection 66%.
33% of BS followed by hospital admission within 2 years: most considered 'mild', 3 (7%) considered 'serious': 2 bowel perforations requiring laparotomy, 1 Petersen´s space hernia requiring laparotomy. Favorable outcomes.
Limitations
Gaps in data collection as loss of follow-up common, reliability of data on occasions questionable as obtained by telephone calls to patients; unable to exclude unidentified deaths as patients operated as early as 1997.
Conclusion
BS is effective long term in our patients. Our results are comparable to those shown elsewhere in the literature.

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EP226

Vitamin D and selected cytokines concentrations in postmenopausal women in relation to metabolic disorders and physical activity

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Introduction
Obesity and metabolic disturbances constitute an important health problem in elderly women. Due to the multifactorial background of these disorders, assessment of the interaction between risk factors is still a significant element of prevention and health promotion in this group. Studies have shown, inter alia, the relationship between low physical activity and vitamin D deficiency with obesity and its complications. Furthermore vitamin D influences production of adipokines and the inflammatory response in adipose tissue.
Subject
The aim of our study was to estimate the association between selected adipokines, vitamin D concentrations, physical activity (PA) and visceral adiposity index (VAI) in postmenopausal women.
Material and methods
The study sample consisted of 318 ethnic homogenous postmenopausal women, aged 50–60. Anthropometric (BMI, WC, WHR) and biochemical (TC, HDL,LDL, glucose, insulin, IL-6, TNFalpha, adiponectin, lutein) measurements and physical activity by IPAQ were performed. Body mass index (BMI), waist-to-hip ratio (WHR) and visceral adiposity index (VAI) were calculated using the standard formulas.
Results
We observed significant negative correlations only between BMI, WC, insulin, HOMA and categorized physical activity. We have shown a negative significant association between leptin and vitamin 25 (OH)D concentrations ($P=0.007$) and positive between adiponectin ($P=0.014$) but we didn't observe significant assiociation with TNF alpha and IL-6.
Conclusions
The results of the multiple linear regression analysis, revealed that vitamin D and HOMA were the factors influencing the concentration of adiponectin and leptin. Vitamin D and HOMA are independent factors significantly affecting leptin and adiponectin levels in contrary to VAI.

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EP227

Study on effect of the tumor necrosis factor–α on onset and progression of obesity in patients with diabetes mellitus

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The fat tissue inflammation and insulin resistance formation are common in obesity and type 2 diabetes mellitus. The tumor necrosis factor–α (TNF-α), a pro-inflammatory cytokine, was found to be a key one in onset and progression of insulin resistance, blocking the insulin signaling pathway and hampering the gene expression of GLUT4, the intracellular insulin-regulated glucose transporter in body tissues. Rise in the TNF-α concentration in blood serum is believed to be associated with the excessive body mass or obesity. TNF-α can be used for diagnosis of diabetes mellitus in the obese patients. The work was initiated to identify associations between TNF-α blood serum levels in the obese patients and risk of diabetes mellitus onset. There were 3 groups of persons examined. The persons with normal body mass index (BMI) were included into the 1st group, the non-diabetic obese persons with BMI more than 28 kg/m^2 and the diabetic obese persons were included into the 2nd and 3rd group, respectively, for the anthropometric and clinical-laboratory parameters of the carbohydrate and lipid metabolism to be measured by the enzyme-linked immunosorbent assay (ELISA). The MR-96A Microplate Reader (Shenzhen Mindray Bio-Medical Electronics Co. Ltd., China) was used to perform qualitative or quantitative determination of samples by the photometric measurements. The findings demonstrated that serum TNF-α levels in the non-diabetic obese persons (3.55±0.30 pg/ml) and the obese diabetics (3.96±0.14 pg/ml) were significantly higher than those in the controls (0.79±0.30 pg/ml) and mean standard reference values. Measurements of TNF-α levels in blood sera of the obese persons are important for early diagnosis of main metabolic disorders resulting in T2DM onset.

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EP228

Hyperinsulinemia does not reduce plasma sex hormone-binding globulin levels in obesity

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The liver produces and secretes sex hormone–binding globulin (SHBG), which transports sex steroids and regulates their access to tissues. Body mass index is a major determinant SHBG concentration in the blood of men and women. Low plasma SHBG levels are associated with obesity and predict the development of type 2 diabetes and cardiovascular disease. The reason why obese individuals have low circulating SHBG has been attributed to hyperinsulinemia, but no mechanistic evidence has ever been described. Over the past decade we and others have contributed to gathering evidences that demonstrate that insulin does not regulate SHBG production. We have used *in vitro* (HepG2 cells) and *in vivo* (human *SHBG* transgenic mice) approaches to show that hyperinsulinemia does not reduce SHBG production. We have elucidated the molecular mechanisms by which carbohydrates and proinflammatory cytokines (i.e. tumor necrosis factor alpha and interleukin 1 beta) reduce SHBG production. Importantly we and others have corroborated these results in humans. All these evidences point to the downregulation of *SHBG* mediated by carbohydrates and proinflammatory cytokines as one explanation for the low levels of total sexual steroids that exist in chronic inflammatory diseases such as obesity and type 2 diabetes.

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EP229

Hypertension and diabetic pregnancy: Epidemiological aspects and evolution

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Introduction
High blood pressure during pregnancy is associated with various maternal and fetal complications. This risk further complicates the pregnancy of diabetic women.
Patients and methods
We carried out a longitudinal retrospective study including one hundred pregnant women with type 1 and type2 diabetes, recruited from the patients monitored at the national nutrition institute during the period from January to December 2016.
Aim of the study
Study the epidemiological characteristics of a complicated pregnancy of diabetes and hypertension in a Tunisian center, and describe the maternal and fetal outcome of these risky pregnancies.
Results
The average age of our patients was 32.87±5.3 years, the average pre-gestational BMI was 28.2±6.48 kg/m^2, 63.6% of the patients were overweight. The majority (70%) of patients had unbalanced pre-conception diabetes (HbA1c>7%). Twelve percent of the patients had a history of high blood pressure. During pregnancy, 17.6% of women were on anti hypertensive therapy (calcium antagonists: 12.4%, beta blocker: 3.1%, central antihypertensive: 2.1%). Only 2.1% of patients presented with pre-eclampsia. For the glycemic parameters, a significant improvement in HbA1c was observed in the 2nd trimester, which was maintained during the 3rd trimester. Patients had reduced their HbA1c in the 2nd trimester by 1.58% compared to pre-conceptual HbA1c ($P<10^{-3}$). The outcome of the pregnancy was favorable with full-term delivery in 72% of the cases. Premature delivery took place in 15% of cases, Therapeutic termination of pregnancy in 1% of cases, early spontaneous abortion in 8% of cases, late abortion in 1% of cases and stillbirth in 3% of cases. The majority (93.3%) of our patients delivered by cesarean. The main causes of cesarean delivery were foetal distress (29.6%), macrosomia (23%) and history of a scar uterus (18.5%). Only 2.4% of caesareans were motivated by pre-eclampsia. The average birth weight was 3577.2±0.72 kg. Macrosomia was observed in 24% of the cases. Five newborns (5.7%) presented neonatal malformations at birth: three cardiac, one urological and one polymalformative syndrome. We found five cases of early neonatal death (5.7%).
Conclusion
Diabetic pregnancy complicated by hypertension is associated with an increased risk of maternal and foetal complications. Pre-conception management and action on modifiable factors could significantly improve the prognosis.

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EP230

Evaluation of neopterin levels in patients with diabetes mellitus

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Background and aims
Diabetes is an endocrinological disease with high incidence and important complications. Studies indicate that by 2030, diabetes will affect approximately 366 million people around the world. Neopterin is produced by activated monocyte-macrophages with the induction of interferon gamma and it is accepted as a biomarker of immune activation. Elevated neopterin levels in biological fluids can be observed in neurological, cardiovascular and autoimmune disorders, different types of malignancies and infections. The aim of this study was to evaluate the possible changes of serum and urinary neopterin levels in diabetes patients.
Materials and methods
36 patients with type I diabetes mellitus, 33 patients with type 2 diabetes mellitus and 30 healthy controls were recruited the study. The patients with type 2 diabetes mellitus were further subgrouped according to their drug therapy (15 metformin treatment and 18 metformin+vildagliptin treatment). Serum and urinary neopterin levels were determined by ELISA and HPLC, respectively.
Results
In all groups, serum and urinary neopterin levels were found to be correlated. All groups represented higher neopterin levels compared to controls. Although patient levels were higher, no statistical significance was observed among study groups. The highest levels were observed in metformin medicated patients with type 2 diabetes mellitus.
Conclusion
The study pointed out that neopterin levels increase in diabetes patients. The change is also possible in different types of diabetes and different antidiabetic agents. Further studies with increased number of patients are required to confirm these results.

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EP231

Anxious and depressive reactions among diabetic patients in Belarus: Prevalence and impact on behavior associated with type 2 diabetes

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Background
The number of patients with type 2 diabetes with mental problems will increase in the coming years[1]. The fight against diabetes cannot be reduced only to the competent prescription of medications, but should be carried out comprehensively taking into account numerous barriers.
Aims
The objective of this study was to investigate prevalence and impact of anxious and depressive reactions among persons living with type 2 diabetes in Belarus to improve the support system for diabetic patients.
Method
Screening for type 2 diabetes was done in different population groups. A total of 90 participants with previously diagnosed type 2 diabetes and 90 adults without diabetes were recruited. The GAD-7 scale and the PHQ-9 scale were used to determine the level of anxious reactions and the level of depressive reactions; glycated hemoglobin was used to analyze the effectiveness of the hypoglycemic therapy.
Results
Of the 90 patients examined, more than 70% showed anxiety reactions and 45% showed depressive reactions. Patients with anxiety and depressive reactions had poor self-care skills and had poor glycemic control. Of the total diabetic patients only minority had adequate blood glucose testing practices.
Discussion
We cannot do without new pharmacological treatments for diabetes. But if you look at the entire success story of diabetology, it becomes clear that this is not enough. The North Karelia Project[2] was able to achieve results in the fight against cardiovascular diseases when pharmacological discoveries did not reach modern heights. And this means that 1) an integrated approach in the treatment of chronic diseases can bring good results; 2) the impact on society as a whole, can change the behavior of even weakly motivated patients; 3) with an integrated approach to the treatment of diabetes, it is important to consider the psychological status of patients.
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Keywords: anxious, depression, diabetes education, psychotherapy empowerment, self-management, care management, chronic care, diabetes mellitus, disease management program.
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EP232

The effects of hypoglycemic therapy on the sleep apnea in patients with type 2 diabetes mellitus

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Type 2 diabetes mellitus (DM2) is often associated with obstructive sleep apnea (OSA), according to the literature. Current approach in choosing the hypoglycemic therapy is based on individualization, but do not take into account the effect on OSA. The research purpose: to evaluate the effect of various hypoglycemic agents on the characteristics of OSA in patients with type 2 diabetes.
Materials and methods
The study included patients with OSA and DM2, that were divided into 2 groups depending on hypoglycemic therapy (without CPAP therapy). Group 1 ($n=12$) included patients using metformin+ gliclazide MR in treatment and group 2 ($n=14$) included treatment using empagliflozin+metformin. During the study, all patients were twice monitored for glycated hemoglobin (HBA1c), weight, body mass index (BMI), polysomnographic indicators (PSG) (SOMNOlab2, Weinmann R&K (Germany)). Patients follow-up was 6 months.
Results
Patients of groups 1 and 2 are comparable in terms of experience of DM2 (6.0 [5.0; 8.0] vs 7.5 [5.9; 8.1] years), age (43.0 [37.0; 46.0] vs 45.0 [39.0; 47.0] years), (BMI) (35.0 [33.1; 36.6] vs 34.7 [33.1; 35.1] kg/m²), HBA1c (8.0 [7.6; 8.6] vs 8.3 [7.6; 8.9]%), respectively. To assess the severity of OSA according to the results of PSG, the following was defined: apnea-hypopnea index (AHI) in group 1–25.7 [23.1; 27.2] patients vs 24.1 [21.5; 25.2] patients in group 2, which corresponded to OSA of moderate severity cases. The degree of blood oxygen saturation (SpO2) 78.0 [74.1; 80.2]% vs 84.2 [75.1; 88.2]% ($P=0.05$). Repeated investigations, after 6 months, demonstrate decreasing HBS1c in group 2 to 7.1%, BMI to 32.2 [30.1; 33.0] kg/m² and PSG characteristics. AHI parameter 26.8 [24, 1; 34.2] patients vs 12.0 [11.1; 14.2] patients ($P=0.02$), the average duration of SA is 34.7 [29.1; 38.2] vs 14.1 [12.8; 16, 2] ($P<0.01$), SpO2 –76.1 [75.1; 80.2]% vs 89.0 [88.0; 94.2]% ($P<0.02$) in comparison groups 1 and 2, respectively.
Conclusion
The administration of metformin (2500 mg/day) in combination with empagliflozin (10 mg/day) treatment in patients with DM 2 and OSA for 6 months is accompanied by reduction of episodes duration and decreasing in the severity of OSA, an increasing in SpO2 and also improvement in HBA1c, decreasing in BMI.

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EP233

Diabetes and ramadan: Analysis of the behiavor of tunisian patients towards treatement

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Introduction
Fasting during Ramadan is an obligatory practice for adult Muslims. Although exemptions exist in certain conditions,including diabetes, the majority of diabetic patients fast despite this concession with the risk of complications mainly hypoglycemic accidents. The aim of this study is to establish the relationship between hypoglycemic accidents and drug treatment, therapeutic education, clinical and biological characteristics of tunisian diabetic patients during Ramadan 2019.
Methods
A prospective descriptive observational study including 85 diabetic patients followed at the National Nutrition Institute of Tunis. Clinical and biological data are noted before four to eight weeks and after the month of Ramadan 2019.
Results
The mean age was 55.8±12.7 years. Most of the patients had type 2 diabetes (97.7%). A slight female predominance was noted (52.3%). The average duration of diabetes was 10.6±6.6 years. Two thirds of the patients are classified as high or very high risk for fasting. Only 30% of the patients were allowed to fast. Treatment with oral antidiabetics, insulin, or a combination of the two was prescribed in 50%, 12.8% and 37.2% of cases. The average of HB1AC before and after Ramadan was 8±1.2%, and 8.6±1.35% respectively. Severe hyperglycaemia (> 3 g/l) was reported in 5.8% of cases. Hypoglycemic accidents were noted in 18.6% of patients, 14.9% of whom were on insulin ($P=0.026$), either alone or in combination with oral antidiabetics, 16.27% were at high or very high risk ($P=0.128$), 87.5% with type 2 diabetics ($P=0.03$) and 13.95% uneducated for fasting ($P=0.82$). Most of patients fasted all month (72.1%). Hypoglycemic accidents were the main cause of breaking fasting (62% of cases, $P<0.01$). Half of the patients did not glycemic monitoring during the fasting but without significant impact on the incidence of hypoglycaemia. In addition, there were no hospitalized patients during this month.
Conclusions
The consequences of fasting in diabetic patients were mainly hypoglycaemia. Insulin therapy was a predictor of hypoglycemia during Ramadan. Identification of individuals who required Ramadan specific education is essentiel to prevent these complications.

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EP234

Treatment goal achievement in patients with type 1 diabetes mellitus followed-up at a tertiary center in greece

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Aim
Current guidelines for type 1 diabetes mellitus (DM1) suggest a therapeutic goal for glycosylated hemoglobin (A1c) of <7.0% in adults and <7.5% in children and adolescents, while emphasizing the importance of managing dyslipidemia. We aimed to record the achievement of therapeutic goals in DM1 patients followed-up in a Greek tertiary center.
Methods
Data were included from DM1 patients who had visited the Department at least once in the previous two years. The most recent and mean A1c value over the previous two years, body mass index (BMI), systolic and diastolic blood pressure (SAP, DAP) and lipids were recorded. Results are reported as mean (standard deviation, range).
Results
Data were included for 157 out of 616 patients; 119 adults (≥18 years) and 38 children or adolescents (< 18 years). In adults, mean age was 37 years (14, 18–70), and the most recent and mean A1c were 7.6% (1.3, 4.6–12.5) and 7.7% (1.4, 4.6–11.7) respectively. A1c <7.0% was achieved in 34% of patients. Mean BMI was 25 kg/m^2 (5, 17–39), with 25% being overweight and 19% obese. Combined SAP/DAP <140/90 mmHg was observed in 78% of patients. Total cholesterol (TC) was 188 mg/dl (43, 108–391), LDL 112 mg/dl (34, 45–200), HDL 57 mg/dl (14, 25–100) and triglycerides (TG) 99 mg/dl (137, 26–1436), whereas LDL <100 mg/dl was observed in 42% of patients. The combined treatment goal of A1c <7.0%, LDL <100 mg/dl and SAP/DAP <140/90 mmHg was achieved in 6.4% of patients. In patients <18 years, the mean age was 13 years (3, 6–17), BMI 20 kg/m^2 (4, 15–35), the most recent A1c 7.4% (1.2, 5.6–11.8) and the mean A1c 7.4% (1.7, 5.4–10.3). A1c <7.5% was achieved in 69% of patients. SAP was 110 mmHg (11, 90–129), DAP 70 mmHg (7, 60–84), TC 174 mg/dl (29, 121–259), LDL 98 mg/dl (25, 49–150), HDL 58 mg/dl (13, 39–88) and TG 84 mg/dl (60, 25–298). Insulin pump therapy was used by 26% of adults and 21% of children or adolescents. In these patients, A1c improved after pump use from 8.0% (1.8, 5.1–11.7) to 7.2% (1.1, 4.6–10.2) while the most recent A1c was 7.3% (1.1, 4.6–10.5).
Conclusions
Despite recent progress, a significant proportion of DM1 patients do not reach the therapeutic goals for glycemic, lipid and blood pressure control, whilst many are overweight or obese. Insulin pump use is associated with a sustained improvement in glycemic control.

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EP235

Flash glucose monitoring in type 1 diabetes: Real world data

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Introduction
Clinical trial data demonstrate improved glycemic control in individuals with type 1 diabetes (T1D),especially, reduction of time in hypoglycaemia with flash glucose monitoring (FGM);however real-life conditions can modify this scenario.
Aim
To examine real world use and glycemic control following a standardized initiation process of FGM.
Methods
Individuals aged 18 years or older with T1D were prospectively recruited from consecutive visits in our outpatient clinic. Pregnancy, diabetic ketoacidosis or use of continuous glucose monitoring (CGM) in the previous 6 months were exclusion criteria. CGM metrics from baseline (first 14 days of use) and 12 months were compared. Subgroup analysis by sex was performed. The clinical targets for CGM established in the 2019 ATTD consensus were used.
Results
Thirty individuals were included (56.7% males); mean age of 49.6±13.2 years and diabetes duration of 26.2±12.4 years; 90% were on multiple daily injections and the remainder on insulin pump therapy. Forty-seven percent (n=14) had at least one established T1D chronic complication. Mean HbA1c was 7.7±1.1% and 7.5±1.2% at baseline and 12 months, respectively (P=0.153) Mean time in range (TIR) was 50.9±17.1% and 56.5±17.3 at baseline and 12 months, respectively (P=0.113). At baseline 10.7% reached the goal of TIR >70%, rising to 20% at 12 months (P=0.003). Mean time above range (TAR) had a similar evolution, from a median of 43.6±18.2 to 38.2±19.2 at baseline and 12 months, respectively (P=0.188). At baseline, 14.3% of the individuals had a TAR <25%, compared to 23.3% at 12 months (P=0.011). There was no difference neither in time below range (TBR) nor on duration or percentage of level 2 hypoglycemia. A severe hypoglycemia event in the previous 6 months was reported by 16.7% of the patients at baseline, compared to 3.3% at 12 months. Median number of scans per day was 7.0 (IQR 5.0) and 8.0(6.0) at baseline and 12 months, respectively (P=0.066). In the analysis by sex,the percentage of male individuals attaining their TIR and TAR goals increased from 6.7% at baseline to 23.5% at 12 months (P=0.038) and from 13.3% at baseline to 35.3% at 12 months (P=0.012), respectively; no statistical difference found on TBR. In the female group no difference was found on the proportion of individuals reaching their CGM goals.
Discussion
At 12 months, there was an increasing number of individuals who reached the CGM targets for T1D while also reducing severe hypoglycemic events. Our data support the benefit of FGM on glucose control in T1D.

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EP236

Type 1 diabetes and challenges ahead

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The incidence of type 1 diabetes mellitus (T1DM) is rising. The demands of daily management, blood glucose variability and potential complications pose challenges in management of T1DM.
The aim of this study was to determine the clinical and metabolic profiles of T1DM patients attending Midland Regional Hospital Portlaoise diabetes service in 2017 and to assess their microvascular and macrovascular complications.
A retrospective analysis of data of 106 patients with T1DM was performed. Mean age of the patients was 39.9±14.4 years, 60.4% were males, and mean duration of diabetes was 15.5±12.9 years. 39.6% were overweight (BMI 25 to <30 kg/m^2) and 24.5% obese (BMI ≥30 kg/m^2). 19.8% had HbA1c <53 mmol/mol, 25.5% had HbA1c 53 to 63 mmol/mol, 30.2% had HbA1c 64 to 75 mmol/mol and 24.5% had HbA1c >75 mmol/mol. 66% were within blood pressure target (< 140/90 mmHg). 103 of patients used basal bolus insulin regime, 2 on premixed insulin and one on insulin pump. Only 10.4% did carbohydrate counting to adjust insulin doses. 20.8% had documented hypoglycaemic unawareness. 25.5% had microalbuminuria, 21.7% had background retinopathy, and 11.3% had proliferative retinopathy. Nine were at moderate risk for diabetes foot disease, four at high risk and one had active foot disease.7.5% had coronary artery disease. Our preliminary data demonstrated that overweight/obesity is common and suboptimal glycaemic control and hypoglycaemic unawareness remain significant challenges in our T1DM cohort. Resources to improve T1DM self-management education programmes are essential and use of continuous glucose monitoring and insulin pump in selected patients may overcome these challenges.

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EP237

Metabolic markers of persistent hyperglycemia

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Introduction
The actual prevalence of early carbohydrate metabolic disorders is associated with persistent hyperglycemia and can only be detected by targeted screening.

Objective
We examined 316 people aged 51.21(46.7;62.35) years, without DM.
Methods
We determined the 10-year risk of T2DM according to the Findrisc scale, anthropometric data, lipid profile, glycemia and HbA1c level, linear dimensions of preperitoneal and subcutenous fat by ultrasonography methods. HbA1c ≥ 6.5% was determined as persistent hyperglycemia marker.
Results
Among 316 examined, 13 patients had glycemia 5.6–6.9 mmol/l (4%), 11 patients had glycemia ≥7.0 mmol/l (3.6%), and 18 patients had HbA1c ≥6.5% (5.7%). According to Findrisc scale: below 7 points – 20%, 7–11 points – 48%, 12–14 points–13%, 15–20 points – 15%, more than 20 points – 4%. Among 60 people (≥15) after additional glycemia and oral glucose tolerance tests, T2DM was first diagnosed in 12 people (3.7%), prediabetes in 26 people (8.2%), of which impaired fasting glucose tolerance (IFG) – in 10, impaired glucose tolerance – in 16. Hyperglycemia development was significantly affected by an increase in the linear dimensions of preperitoneal fat ($b=0.62$; Exp(b)=1.86(95% CI=1.063.28); $P=0.03$); increase of LDL and LDL-C ($b=1.21$; Exp(b)=3.36 (95% CI=1.666.82) $P=0.001$) and atherogenic index (AI) ($b=0.40$; Exp(b)=1.49 (95% CI=1.131.20); $P=0.005$). Increase of BMI and triglycerides increased the risk of persistent hyperglycemia at a steady tendency level. Statistically significant risk of developing persistent hyperglycemia was obtained with LDL-C > 1.6 mmol/l:R-$R_{LDL\text{-}C\geq 1,6}$=5.51(95% CI=2.33 ÷ 13.05); AI > 2.55:$RR_{AI\geq 2,55}$=3.22(95% CI=1.36 ÷ 7.62). For the linear size of preperitoneal fat, the RR indices were at the level of steady tendecy $RR_{ППДК\geq 1,75}$=2.22 (95% CI=0.84 ÷ 5.83; 90% CI=1.00 ÷ 4.99). It is noteworthy that the critical cutoff points of all indicators of the lipid profile lay in the range of reference values.
Conclusion
For T2DM screening, a Findrisc survey is justified, in spite of normal lipid profile values, ultrasonography of adipose tissue is required.

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EP238

Psychological peculiarities of parents of children with diabetes mellitus

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Introduction
The primary incidence of T1DM in children in Belarus is 19.27‰. It's noteworthy, modern training programs of Schools of Diabetes include questions of the psychological state.
Objective
The study included 26 parents of children diagnosed with T1DM.
Methods
we used questionnaire to assess the attitude of parents to child's disease, HADS and social adaptation self-evaluation scales (T. Holmes, R. Ray).
Results
High scores characterize anxious attitude of most parents (78%) to the child's disease. 54% of parents showed external parental control of the disease when the causes of disease are seen as something out of the parents' control. 27% of parents indicated hypernosognosia (exaggeration of the severity of disease), 13% – hyponosognosia. 15% of parents showed low indices for internal control, when parents perceive themselves as fully responsible for the child's disease. In 3 cases (1.16%) parental anxiety that exceeded subclinical indicators was revealed, in 1 case – clinically expressed depression, which was most likely not associated with the child's disease. Almost all of the studied (96%) had problems with controlling the physical activity of the child; 2% of parents, on the contrary, indicated high activity control indices characterizing the setting of maximum restrictions on the activity of the child. It should be noted that parents whose anxiety was below average (13.6%) tried to replace anxiety with something else: emotional lability, apathy, obsessions, etc., which further may negatively affect the psychological health of parents and their children.
Conclusion
When a problem raises in the family, the child and parents need the qualified help of a psychologist in order to cope with acute stress and begin to make joint decisions objectively.

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EP239

Mauriac syndrome – type 1 diabetes, nanism and more

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Introduction
Mauriac syndrome is characterized by delayed growth and development, obesity, hepatomegaly and elevated transaminases in type 1 diabetes mellitus (T1DM) patients who have poor glycaemic control. Usually recognized in adolescence, when growth failure and pubertal delay became notorious.
Case Report
A 19-year-old male was referred to the Endocrinology Department due to short stature. He was severely distressed about his stature and younger appearance which were negatively impacting his search for a job. The boy was diagnosed with type 1 Diabetes Mellitus (T1DM) at age 2. Records showed no history of ketoacidosis, average A1c 9–11%, GFR 98 ml/min/BSA. He was visiting the diabetologist every 3 months. There were no other relevant antecedents. He was proportionate, had a non-syndromic phenotype and seem to be 15 years old. He measured 154 cm (–3.06 SDS WHO), BMI 19.8 kg/m^2 (–0.87 SDS WHO) at age 19. Predicted adult height was 181 cm. He was Tanner stage 4 (G4P4Ac) with testicles of 25 ml bilaterally and bone age was delayed –3.5 years. From records of the past 4 years we extracted constant bone age delay around –3 years. Puberty had started at the chronological age of 15 and progressed according to bone age but there was no growth spurt. From age 16 he grew per year 2.5 cm, 1 cm, 0.5 cm. Routine tests for the investigation of short stature were normal except for low IGF-1 for age, sex and even when adjusted for Tunner stage and bone age (92 ng/ml RR 243–527). There was an adequate response to provocative testing (GH > 10 ng/ml). Selar RMI was normal. Abdominal US confirmed steatosis and dual-energy x-ray absorptiometry documented compromised bone health with a lumbar and femoral score of –4.1 and –3.3 respectively. Despite patient education and several attempts to intensify and optimize glycaemic control, there were no significant changes on A1c nor in IGF1 levels. He grew 0 cm during the last year.
Conclusions
Our report alerts physicians for the developmental complications associated with insufficient management of diabetes mellitus. The adequate management of T1DM in adolescents is very challenging and once the struggling adolescent is confronted with severe and possibly irreversible complications of the disease the challenge is made harder. Precocious patient education with familiar involvement through childhood should be mainstream. Mauriac syndrome is severe and although reversible with good and sustained glycaemic control, the best intervention strategy is it's prevention.

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EP240

Metabolic profile of adolescents with type 1 diabetes in tunisia (about 102 cases)

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Background
Type1 diabetes is the third most common chronic illness in childhood following asthma and cerebral palsy. Adolescence is characterized by physical and psychological changes and there is global evidence suggesting that metabolic control deteriorates during the period of teenage.
Aims
To study the characteristics of a group of Tunisian adolescents with type 1 diabetes and describe the various metabolic complications observed.
Methods
Cross sectional study concerning 102 adolescents with type 1 diabetes hospitalized or followed at the consultation of diabetology of the Institute of Nutrition in Tunis over a one-year period between January 2017 and January 2018.
Results
The study population consisted of 102 adolescents with type 1 diabetes. 51% were female (sex ratio=0.96). Participants classified underweight (UW) were 3(2.9%), those of normal weight (NW) were 82 (80.4%), overweight (OW) 10 (9.8%) and obese (O)7 (6.9%). Abdominal obesity was present in

21.6% of our patients with a significant female predominance (girls:34.6%, boys:8%, $P<10^{-3}$).
The mean duration of diabetes was 7.1±4.3 years. The majority (78.9%) of our patients had an HbA1c level>9%. Therapeutic adherence was low in 29.4%. Insulin omission was present in 7.8% of patients (girls: 11.5% vs boys: 4%; $P=0.2$). Diabetic retinopathy, nephropathy, and neuropathy were found respectively in 3.9%, 5.9%, and 5.9%. Moderate and severe hypoglycemia rate in the past 3 months were respectively 11.8±16.2 and 1.8±7.9 per month. The average number of ketosis or Ketoacidosis decompensations in the last year was 3.6±6.3 per year. The average number of hospitalizations per year was 2.2±1.9. The average length of hospital stay was 9.2±5.1 days. Dyslipidemia was diagnosed in 30.4% of diabetics with a significantly higher frequency in girls (girls: 38.5% vs boys: 22%; $P=0.05$). The school failure rate was high (50%) in our series.
Conclusions
Metabolic control of type 1 diabetes is difficult during adolescence due to hormonal fluctuations. Ketoacidosis decompensations and severe hypoglycemia are the most common complications in adolescents with type1 diabetes and may affect the academic performance of these young people by increasing the frequency of hospitalizations. Additional efforts are needed to improve the quality of care for young diabetics.

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EP241

Management of diabetic Adhesive capsulitis in physical medicine and rehabilitation

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Introduction
Adhesive capsulitis (AC) is a condition characterized by spontaneous onset of shoulder pain and gradual loss of active and passive shoulder motion. This condition is more common in people with diabetes. The aim of this study was to appreciate the contribution of different therapeutic means used in physical medicine and rehabilitation (PMR) in the management of AC in Diabetic patients.
Patients and methods
A retrospective study was conducted during the period from January 2015 to January 2018. Diabetic patients diagnosed with AC in PMR department were included. All patients' demographic data, dominant hand, affected hand and history of relevant co-morbidities were noted. Passive flexion, abduction, and external and internal rotation range of motion (ROM) were reported. Pain was evaluated using Visual Analog Scale (VAS). Therapeutic protocol was noted and assessments were made at baseline (before the first treatment session) and after 3 months of physical therapy.
Results
Forty diabetic patients with AC were included. The mean age was 51.2±9 years with a sex ratio of 1.6. All patients benefited from rehabilitation sessions: 1 daily session for a month followed by 3 weekly sessions with an average of 36 sessions. Intra articular corticoid injection was done in 37.5% of cases and 3 patients benefited from guided capsular distension. We noted a statistically significant improvement in pain and ROM in all sectors ($P<0.05$).
Conclusion
Rehabilitation care is beneficial among Diabetic population suffering from AC.

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EP242

Assessment of podiatry risk and correlation with the level of education in diabetics

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Introduction
Diabetic foot trophic disorders and their complications leading to the risk of amputation remain a major public health problem. The objective of our work was to determine the level of podiatric risk in our diabetic patients according to the classification of the International Working Group of the Diabetic Foot (IWGDF) in order to reduce the rate of amputation and study their level of education and correlate it to podiatric risk.
Methods
This is a descriptive and analytical cross-sectional study including all diabetics hospitalized at the National Institute of Nutrition in Tunis for chronic diabetes imbalance, carried out over a period of two months (July – August 2019).
Results
The mean age of the patients was 55.08±14.22 years. The sex ratio was 0.67. The majority of our patients were type 2 diabetics (90.24%). During the clinical examination of the foot, plantar hyperkeratosis was the most noted manifestation (65.85%). Based on the IWGDF classification, 42.68% of patients had a grade 0 podiatric risk. Regarding the overall educational level, 76.83% poorly educated patients and 23.17% educated patients were noted. The overall educational level is significantly associated with the podiatric grade ($P<0.05$).
Conclusion
Therapeutic education or even podiatric education of the patient is important in the prevention of complications of the foot. Patient-centered training in foot care practice in public health facilities would reduce the rate of morbidity and mortality from complicated diabetic foot.

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EP243

Results of the assessment of homocysteine and vitamin B12 basal levels in patients with diabetes mellitus type 1 depending on anxiety level

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Objective to assess homocysteine and B12 basal levels in patients with diabetes mellitus type 1 (DM type 1) depending on anxiety level.
Materials and methods
163 patients with DM type 1 aged 18–65 years. Diabetes duration is 11.18 [4.28; 22.33] years. The level of anxiety was assessed according to the HADS scale. The homocysteine and vitamin B12 level in serum was determined. Depending on the anxiety level according to the results of the HADS score, patients were divided into 2 subgroups.
Results
The median HC level in serum in patients with anxiety was 13.29 [8.80; 15.90] mmol/l against the median HC level in patients without anxiety – 9.80 [7.94; 11.50] mmol/l and was higher in patients with anxiety (U=15.12; $P=0.02$). The risk of developing anxiety in patients with DM type 1 is associated with a HC level of more than 15.39 mmol/l (OS=1.21; $P=0.03$; 95% CI 1.06–1.37). The median vitamin B12 level in serum in patients with anxiety was 126 pg/ml [28.0; 473.0] against the median vitamin B12 level in serum in patients without anxiety – 312 pg/ml [168.0; 602.0] and was lower in patients with anxiety (U=14.65; $P=0.04$). A negative correlation was established between the level of anxiety by HADS and the level of vitamin B12 in serum ($r=-0.19$; $P<0.05$).
Conclusion
Patients with anxiety have a higher HC level and lower vitamin B12 level than patients without anxiety. With a decrease in vitamin B12 level, an increase in anxiety level by HADS is noted. The risk of developing anxiety in patients with DM type 1 is associated with HC level in serum above 15.39 mmol/l.

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EP244

Relationship between indicators of androgenic status and renal function in patients with diabetes mellitus type 1

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Objective
To analyze correlation between the duration of diabetes mellitus (DM), renal function and androgenic state indicators in patients with DM type 1. 175 males with DM 1 type in the age of 18–55 years (39.75±9.69) with the duration of disease more than 1 year were examined. The control group included 25 almost healthy males in the age 21–41 years (34.60±7.80).

The compensation of DM was estimated by the level of glycosylated hemoglobin (HbA1c). Also, the indicators of lipid profile (total cholesterol, triglycerides), glomerular filtration rate (GFR) MDRD, total testosterone, luteinizing hormone/follicle-stimulating hormone (LH/FSH), prolactin, sex hormone-binding globulin, homocysteine. The statistical analysis was conducted with the use of SPSS 17.0. It was defined that there was the decrease of GFR according to the formula MDRD in the terms of the increase of diabetes duration: in the group with GFR < 60 ml/min/1.73 m^2 the duration of the diabetes was 23.72 years (± 8.04), in the group with GFR > 60 ml/min/1.73 m^2 it was12.15 years (± 8.37) ($P < 0.05$). In the terms of the decrease of GFR the increase of correlation FSH/LH was defined: in the group with GFR < 60 ml/min/1.73 m² the correlation LH/FSH was 1.82 (± 0.63), in the group with GFR > 60 ml/min/1.73 m² it was 1.37 (± 1.26) (< 0.005); the decrease of the total testosterone: in the group with GFR <60 ml/min/1.73 m² the total testosterone was 9.90 nmol/l (± 3.10), in the group with GFR > 60 ml/min/1.73 m^2 it was 10.61 nmol/l (± 8.76) ($P < 0.05$); the decrease of the homocysteine level was noticed: 11.42 ± 2.70 mcmol/l comparing with the10.32 ± 4.92 mcmol/l in the group with GFR > 60 ml/min/1.73 m^2 ($P = 0.006$). We have not revealed any differences in the level of prolactin, sex hormone-binding globulin. The revealed changes are important risk factors for development and progression of vascular complications and require appropriate arrangements.

Keywords: diabetes mellitus type 1, GFR MDRD, androgenic state.

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EP245

Does 25-OH vitamin D concentration correlate with adipocytokines inpatients with non-functioning adrenal incidentalomas – preliminary study

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Introduction

Vitamin D has pleiotropic effect on human body. Several studies showed that vitamin D deficiency has an influence on inflammation status in endocrine diseases (PCO-S, Graves disease, autoimmune endocrine disorders) and could reflect body fat tissue contain. Both, resistin and leptin, show pro-inflammatory effect.

Aim

The aim of the study was to asses resistin and leptin serum concentration and its relationship with 25-OH vitamin D concentration in patients with non-functioning adrenal incidentalomas.

Material and methods

25 patients hospitalized in Endocrinology City Hospital in Piekary in 2015 with non-functioning adrenal incidentalomas were inclued to the study. The exclusion criteria were: other adrenal disorders, decompensated diabetes defined as HBA1C% > 7, kidney failure as eGFR < 60 ml/min/1.73 m^2, liver failure as bilirubin > 2 mg/dl, INR > 1.5 and albumins < 3.5 g/dl, severe inflammation, cancer therapy. Patients blood was centrifuged, serum obtained and the resistin and leptin concentration determined in duplicates by ELISA method, as per manufacturer's recommendations. Data of vitamin D concentration was taken from patients medical record.

Results

In analyzed group of patients the average vitamin D concentration was 22.9 ng/dl, resistin 6.4 ng/ml and leptin 70.4 pg/ml, BMI 29.9 kg/m^2. With increasing vitamin D concentration, leptin serum concentration decreased ($r = –0.56$, $P < 0.05$) and resistin serum concentration was statistically higher ($r = 0.68$, $P < 0.05$). There was also positive correlation observed ($P < 0.05$) between leptin and anthropometric indicators: BMI ($r = 0.82$), WHtR ($r = 0.73$), BRI ($r = 0.73$), WC ($r = 0.6$), LAP ($r = 0.48$).

Conclusion

Serum 25(OH)D3 concentration in studied group was below range and defined as mild insufficiency. Vitamin D concentration correlates with leptin and resistin in patients with non-functioning adrenal incidentalomas. To confirm obtained results further studies are needed.

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EP246

Metabolic abnormalities of obesity were more severe in men than in women

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Background

Obesity is worldwide epidemics and the main risk factor for many diseases. Traditional methods of prevention and treatment of obesity often unfavorable and patients undergo to alternative treatment such as bariatric surgery. To better understanding the pathogenesis of obesity, we aimed to analyse the main abnormalities in blood serum in patients accepted to bariatric surgery.

Material and methods

27 patients (13 men and 14 women) with obesity after unfavorable treatments were accepted to bariatric surgery. In both group blood fasting and postprandial glycemia, HbA1c level, serum creatinine (Crea), fibrinogen (Fib), ALAT, ACAT, bilirubin, blood urea nitrogen levels, prothrombin index (PTI), lipids level such as Triglycerides (TG), Cholesterol Chol), LDLP, HDLP were measured and compared.

Results

Showed that even average ages were similar in men and women (37 years old), BMI was higher in men (48.09 ± 9) than in women (38.85 ± 5.85). Blood bilirubin (by 1.3 times), Crea (by 1.6 times), ALAT (by 2.1 times) levels were higher in men than in women and showed linkage with BMI. Although the blood coagulation assessed by Fib and PTI, and blood lipids assessed by TG, Chol, LDLP, HDLP levels, as well as the atherogenic coefficient were comparable in both groups, impaired glycemia was determined in 62% of man and in 46% woman. These results suggest that obesity degree, and its metabolic abnormalities were more severe in men than in women.

Conclusion

Metabolic abnormalities were more severe in men than in women with obesity accepted to bariatric surgery after unfavorable treatment and differs by higher BMI, higher blood bilirubin, Crea, ALAT level and more cases of impaired Glycemia (62% vs 42%).

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EP247

Profile of diabetic patients received in the emergency department during the month of ramadan in Mohammed VI university hospital of Marrakech

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Ramadan is a holy month in the Muslim religion, it involves a period of daily fasting from sunrise to sunset, which means an average of fifteen hours of fasting during the day (twelve to eighteen hours depending on seasons and regions). In diabetics, this involves metabolic disorders related to fasting, food mode (quantitative and qualitative change in dietary intake). The objective of our study is to define the profile of diabetic patients seen in the emergency department and referred to the endocrinology, diabetology unit of Mohammed VI university hospital of Marrakech.

Patients and methods

It's about an observational and descriptive study which takes place from May 7th to June 6th 2019, first in the emergency department then in the endocrinology, diabetology unit when patients are referred to. Our population of study is about type 1 and type 2 diabetics, with a duration of fasting from a few hours to fifteen hours a day. The variables studied: a month before and during the month of Ramadan (age, sex, type of diabetes, duration of evolution, anti diabetic treatment, fasting, type of metabolic emergency,complications and comorbidities of diabetes mellitus).

Discussion

2 times more hospitalizations during Ramadan than before.

- Hyperglycemia with or without ketosis: the most frequent decompensation, the frequency of hypoglycemia isweak;

- 22% of T1D fasted more ketosis pdt Ramadan hypoglycaemia
- 53% of T2D fasted: same frequency of hyperglycemia and ketosis but more hypoglycaemia during Ramadan,; 2 times more patients on sulfonamides consulted during Ramadan.
  - HYPERGLYCEMIA: excessive and unjustified discontinuation or reduction of insulin doses and/or ADO; non adherence to dietary instructions, increased calorie intake and in fast sugars? 2 to 3 meals in the space of 8 hours between ftour and shour, snacking…
  - HYPOGLYCEMIA: the periods of low blood sugar are often asymptomatic so underestimatedduring Ramadan.

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EP248

Clinical profile of women with gestational diabetes admitted to day hospital

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Introduction
Diabetic pregnancy is a high risk pregnancy. The objective of our study was to study the clinical-biological profile of pregnant women with gestational diabetes.
Methods
It was a retrospective study of 82 pregnant diabetic women admitted to the day hospital of the National Nutrition Institute in Tunis for the management of gestational diabetes. All patients received regular follow-up until delivery.
Results
The average age of our population was 33.55±4.3 years. On admission, the mean term was 25.6±8.4 years. Pregnancy was scheduled in 12.6% of the cases. 5% were smoking and 2.6% were hypertensive. The average HbA1c was 6.2±0.5%. Hypochromic microcytic anemia requiring iron supplementation was noted in 48% of cases. The diagnosis of hypothyroidism was made in 4.4% of the population studied at an average term of 10 SA requiring the administration of 25 mg/d of L-Thyroxine. Only three of them required an increase in dose to 50 mg/day. Isolated hypothyroxinemia was noted in 5.2%. All the patients required hygieno-dietetic rules and the use of insulin therapy was noted in 26.3% of the cases.
Conclusion
Regular monitoring is essential when diagnosing gestational diabetes in order to maintain a strict glycemic balance throughout pregnancy and to prevent the appearance or worsening of any micro and macrovascular complications.

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EP249

Partial androgen insensitivity syndrome with type 1 diabetes- a case report

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Introduction
Androgen insensitivity syndrome (AIS), also known as testicular feminization, encompasses a wide range of phenotypes that are caused by numerous different mutations in the androgen receptor gene. where there is resistance to androgen actions influencing both the morphogenesis and differentiation of androgen responsive body structures AIS is an X-linked recessive disorder. This disorder includes a spectrum of changes ranging from male infertility to completely normal female external genitalia in a chromosomally male individual that is classified as complete, partial, or mild based on the phenotypic presentation.
Case report
An 18-year-old diabetic,phenotypic female presented to the outpatient endocrinology department with primary amenorrhea. At the age of 13,her mother noticed that our patient's voice became deep & her body hair became more excessive and in abnormal sites (especially above upper lip & chin) with acne.
Physical examination.
Normal vital signs, She had low pitched voice.
Weight: 66 kg/Height:166 cm (US/LS: 0.9) (span:170 cm)/BMI: 24 kg/m^2.
Facial acne Male distribution of body hair:Above upper lip, chin, chest, midline, back (thick, coarse, pigmented).
Breast: Tanner stage 1–2/Pubic hair: Tanner stage 5/External genitalia: clitoromegaly (2 cm).
Severe tenderness on palpation along medial side of inguinal region on both sides.
Hormonal profile: elevated FSH, testosterone with normal LH, Estradiol, PRL.
Δ4-Androstenedione 1.3 ng/ml (N: 0.4–4.5)/Testosterone 6.9 ng/ml (N: 0.1–1).
FSH 90 mIU/Ml (N: 1–12) LH 2.3 mIu/MI (N:1.9–12.5)/prolactin 10 ng/ml (N:2–29 ng/ml).
Trans-rectal US: uterus and ovaries are not visualized/MRI pelvis: Non visualized uterus & ovaries.
Bilateral inguinal ovoid structures are seen representing undescended testes (Rt 2.5 × 2 cm) (LT 2 × 2 cm). karyotyping: The case showing male genotype 100% (46XY).
Conclusion
Androgen insensitivity syndrome is distressing to the patient as well as to the family. Systemic disclosure of the diagnosis in an empathic environment with both professional and family support is encouraged. Patient will be benefited by a multidisciplinary approach including gonadectomy, detailed and repeated psychological counseling along with estrogen replacement. The medical and psychological prognosis for a woman with androgen insensitivity syndrome is excellent if she has appropriate support and counseling.

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EP250

When the diagnosis of degenerative complications precedes that of diabetes

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Introduction
The diagnosis of diabetes often precedes the onset of degenerative complications.
Method
We report the case of a patient who had consulted for a poor foot plantar perforation evolving for 3 months before the diagnosis of diabetes.
Results
He is a 57-year-old active smoking patient with a family history of diabetes and hypertension who presented to the emergency department of the Tunis National Nutrition Institute for inaugural diabetic ketosis with a 'lesion' of the foot evolving for 3 months which does not heal. On examination, he had a BMI=27.4 kg/m^2, stable hemodynamic constants, an uninfected plantar neuropathic ulcer, and neuro-ischemic feet. In biology he had an HbA1C=13.1%, a clearance creatinine=102.5 ml/min (CKD-EPI). He did not have a biological infectious syndrome. The ophthalmological examination had diagnosed diabetic retinopathy. The patient was put on insulin therapy associated to metformin.
Conclusion
In our case, the appearance of the plantar neuropathic ulcer preceded the diagnosis of diabetes by 3 months. Screening for diabetes in people at risk should be systematic to avoid such cases.

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EP251

Ketotic decompensation in diabetics

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Objective
Diabetic ketosis is very often a reason for emergency consultation in diabetics. The objective of our study was to assess the etiologies of ketotic decompensations in diabetics.
Methods
It was a descriptive cross-sectional study of 80 diabetics hospitalized at the National Institute of Nutrition for ketotic decompensation. Each patient underwent a clinical examination with a standard biological assessment.

Results
The average age of the patients was 58.36 years with a male predominance (54%). Diabetes was type 2 in 82% of the cases. The average duration of diabetes was 13.87±4.5 years of which 80.8% were on insulin therapy. The mainly found decompensation factor was an infection observed in 48% of cases. It was a bronchopulmonary infection in 36% of the cases and a urinary tract infection in 32% of the cases. Therapeutic non-compliance or discontinuation of treatment was observed in 22% of the cases. An inaugural ketosis was found in 19% of the cases and an error in the injection sites was found in 3% of the cases. Excessive deviation from diet was noted in 1% of patients. The rest of the cases remain unexplained.
Conclusion
A good education is always beneficial for the diabetic in order to survive with his chronic illness away from complications and stressful situations.

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EP252

Bag of bones: Myth or reality

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Case presentation
73-year-old diabetic, hypertensive and alcoholic Male on treatment for type II diabetes for 25 years, underwent amputation of left great toe and second toe previously had sudden painless swelling of the left foot after a walk. He was diagnosed to have Charcot's foot and had the appearance of bag of bones in CT scan. He was managed conservatively with immobilization and Custom made shoes.
Discussion
Charcot foot is a sudden softening of the bones in the foot that occurs in patients with severe neuropathy and resulting bones are weakened enough to fracture, and with continued walking the foot eventually changes shape. As the disorder progresses, the arch collapses and the foot takes on a convex shape. Charcot foot is a very serious condition that can lead to severe deformity, disability, and even amputation. X-ray examination reveals the appearance of lysis of the bones with marked fragmentation, absence of bone regeneration, the tendency to disarticulation and destruction of the joints and the complete flattening of the longitudinal arch of the foot. The 'club foot' appearance in conjunction with the radiologic findings merits the appellation 'a bag of bones.'[1]

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EP253

Lipid profile in type 1 diabetics

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Introduction
The vascular risk in type 1 diabetics appears to be secondary to the premature development of atherosclerosis.
The objective of this study was to determine the characteristics of the lipid profile of a type 1 diabetic population as well as the different factors that can influence these changes.
Methodology
It was a descriptive cross-sectional study including 30 type 1 diabetic patients, followed at the National Institute of Nutrition in Tunis. Patients underwent a careful clinical examination and a standard laboratory test.
Results
The average age of our population was 26.02±7.90 years. The sex ratio was 1. The age of diabetes was 10.11±5.16 years. The average HbA1c was 10.16±2.1%. The lipid profile was characterized by: hypertriglyceridemia in 8 patients. Hypercholesterolemia in 19 patients. Hypo-HDLemia in 16 patients. We found macroangiopathic complications in 6 of our patients with coronary artery disease and lower limb arteritis; nephropathy, neuropathy and retinopathy microangiopathies were found in 11 patients. The analytical study found no correlation between microangiopathic or macroangiopathic complications and lipid abnormalities in our patients.
Conclusion
In accordance with data from the literature, our study reveals hypertriglyceridemia and hypo-HDLemia characterizing the lipid profile of type 1 diabetics. However, no correlation was found with the degenerative complications noted.

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EP254

Improving diabetes care in children and adolescents with intellectual and developmental disabilities

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Aims
To present an analysis of the evidence related to the prevalence and incidence of diabetes type 1 or type 2 in children and adolescents with intellectual and developmental disabilities, assess available support on managing their diabetes, and the services they receive, investigate the available structured education programs tailored for people with IDD.
Methods
We conducted different searches of multiple databases.
(PUBMED, MEDLINE, PsycINFO, SCOPUS, Web of Science, and Wiley Library) to find relevant articles.
Results
We identified a total of 8 studies: Four studies addressed the prevalence of diabetes in people with an intellectual and developmental disability, Three addressed the impact of diabetes on their health and well-being, and one addressed the available diabetes programs adapted for people with IDD. The prevalence of diabetes in children and adolescents with an intellectual and developmental disability is inconclusive, and the incidence of diabetes in this category is unknown. There is some evidence to support the assumption that children and adolescents with an intellectual and developmental disability might be at higher risk of developing diabetes than their peers. In general, the quality of the evidence on which to base prevention and management strategies is limited.
Conclusions
There are limited studies focused on the prevalence, incidence, and impact of diabetes among children and adolescents with an intellectual and developmental disability. Continuous research is necessary for this field, and especially further studies are necessary to develop new approaches, evaluation tools, educational resources, and diabetes care support services appropriate to the needs of children and adolescents with an intellectual and developmental disability.
Keywords: diabetes, intellectual disabilities, family support, diabetes- management, prevalence, adolescents.

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EP255

Impaired fasting glucose in patients with spondyloarthritis

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Background
Spondyloarthritis is a chronic inflammatory rheumatic disease which may be associated with different comorbidities such as glucose intolerance.
Objectives
Determine the frequency of impaired fasting glucose in a population of patients with spondyloarthritis.
Methods
We performed a cross-sectional study including 50 patients with spondyloarthritis (SA) diagnosed according to ASAS criteria. Fasting glucose was measured for each patient.
Results
The mean age was 44.75±13.5 years. Sex ration(M/F) was four. Clinical phenotypes of SA were: ankylosing spondylarthritis (51.9%),psoriatis arthritis(28%), arthritis associated with inflammatory bowel disease (10%). The mean duration of the disease was 93.27 month. the mean PCR, ESR, PCR-ASDAS and fasting glucose were 29.48, 36.55, 3.38 and 5.62 respectively.

Overweight and obesity were noted in 41.5% of cases.
Eighty-four percent of the patients have a normal fasting glucose,12% of them have a fasting glucose higher than 7 mmol which needs another control to diagnose diabetes and only 4% ($n=2$) have an impaired fasting glucose.
There was no correlation between fasting glucose and these following parameters: PCR-ASDAS ($P=0.745$), PCR ($P=0.291$) and ESR ($P=0.803$).
Discussion
More than 15% of patients with SA have an incorrect fasting glucose including glucose intolerance and diabetes, this pourcentage was higher in psoriatic patients and it was equal to 28.57.
Almost the half of the population are overweight or obese. these two items associated to SA increase the cardiovascular risk.
Conclusion
Identifying glucose intolerance in SA may help physicians to minimize cardiovascular mortality also it can ensure a better quality of life if treated early.

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EP256

Type 2 diabetes in patients with cirrhosis: Prevalence and clinical implications

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Introduction
Disorders of glucose metabolism are often present in chronic liver diseases. The aim of our study is to determine the prevalence and factors associated with type 2 diabetes in patients with cirrhosis.
Methods
This is a retrospective study collecting all patients with cirrhosis between January 2010 and December 2019.
Results
During the study period, 166 patients were included. Of these patients, 47 patients had type 2 diabetes (28.3%). These were 29 women and 18 men with an average age of 61.6 years (between 17 and 84 years). Cirrhosis was metabolic in 18 cases (38.3%), viral B in 9 cases (19.1%), viral C in 8 cases (17%), autoimmune in 5 cases (10.6%), of alcoholic origin in 4 cases and of undetermined etiology in 3 cases. Cirrhosis was classified as CHILD A in 16 patients (34%), CHILD B in 23 patients (49%) and CHILD C in 8 patients (17%). Ascitic decompensation was present in 33 cases (70.2%). Six patients (12.8%) had hepatic encephalopathy. Forty-four patients (93.6%) had esophageal varices on upper gastrointestinal endoscopy. Cirrhosis was complicated by hepatocellular carcinoma (HCC) in 5 patients (10.6%). Analytic study had shown that the presence of type 2 diabetes was associated with older age ($P=0.018$), metabolic origin ($P=0.001$) and viral B origin ($P=0.04$). However, there was no association with gender, the severity of cirrhosis, and the presence of HCC.
Conclusion
In our study, type 2 diabetes was present in 28.3% of cirrhotic patients and it was associated with advanced age, metabolic and viral B origin.

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EP257

Are hospitals in madrid promoting a healthy nutritional environment?

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Introduction
NutriScore is a tool designed with the aim of simplifying the information of the nutritional composition obtained from the labelling. It classifies foods into five colors ranging from green (healthier) to red (less healthy). These colors are associated with five letters (A/B/C/D/E).
Objective
To examine the nutritional value of foods sold in vending machines of the public hospitals in Community of Madrid (Spain), by calculating the nutriscore.
Methods
The study was conducted during the months of January and February 2019. Snacks and beverages sold in vending machines were analyzed. These machines were located in waiting rooms of the emergency departments of every public hospital in the Community of Madrid. The NutriScore of each item was calculated, according to the amount of nutrients in 100 g of food or 100 ml of drink. One obtains the score by punctuating negative elements (caloric value, saturated fat, sugar and sodium) and substracting the positive ones (fruit content, vegetables, nuts, fiber and proteins). The higher this last score, the more unfavourable. According the final result obtained, foods are sorted into one of the five categories.
Results
258 snacks and 92 beverages available in the vending machines of 27 hospitals were analyzed. Snacks were distributed as follows: A 8%, B 5%, C 28%, D 35% y E 24% and beverages: A 1%, B 15%, C 23%, D 26% y E 35%. Category A for drinks only corresponds to water and it was found in 100% of the hospitals. There were only 2 hospitals, 7.4% of the visited, where no drink in Category E was offered. In 4 of the hospitals visited no snack in Category A was offered and in 13 of them more than a 60% were classified into Categories D and E. However, only in one hospital no product classified as E was sold.
Conclusion
Although hospitals should play a role in promoting a healthy lifestyle, the vending machines of the hospitals offer a very high number of products with low nutritional quality.

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EP258

Metabolic markers of persistent hyperglycemia

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Introduction
The actual prevalence of early carbohydrate metabolic disorders is associated with persistent hyperglycemia and can only be detected by targeted screening.
Objective
We examined 316 people aged 51.21(46.7;62.35) years, without DM.
Methods
We determined the 10-year risk of T2DM according to the Findrisc scale, anthropometric data, lipid profile, glycemia and HbA1c level, linear dimensions of preperitoneal and subcutenous fat by ultrasonography methods. HbA1c≥6.5% was determined as persistent hyperglycemia marker.
Results
Among 316 examined, 13 patients had glycemia 5.6–6.9 mmol/l (4%), 11 patients had glycemia≥7.0 mmol/l (3.6%), and 18 patients had HbA1c≥6.5% (5.7%). According to Findrisc scale: below 7 points – 20%, 7–11 points – 48%, 12–14 points–13%, 15–20 points – 15%, more than 20 points – 4%. Among 60 people (≥15) after additional glycemia and oral glucose tolerance tests, T2DM was first diagnosed in 12 people (3.7%), prediabetes in 26 people (8.2%), of which impaired fasting glucose tolerance (IFG) – in 10, impaired glucose tolerance – in 16. Hyperglycemia development was significantly affected by an increase in the linear dimensions of preperitoneal fat ($b=0.62$; Exp(b)=1.86 (95% CI=1.063.28); $P=0.03$); increase of LDL and LDL-C ($b=1.21$; Exp(b)=3.36 (95% CI=1.666.82) $P=0.001$) and atherogenic index (AI) ($b=0.40$; Exp (b)=1.49 (95% CI=1.131.20); $P=0.005$). Increase of BMI and triglycerides increased the risk of persistent hyperglycemia at a steady tendency level. Statistically significant risk of developing persistent hyperglycemia was obtained with LDL-C>1.6 mmol/l:$RR_{LDL\text{-}C\geq 1,6}=5.51$ (95% CI=2.33 ÷ 13.05); AI>2.55:$RR_{AI\geq 2,55}=3.22$ (95% CI=1.36÷7.62). For the linear size of preperitoneal fat, the RR indices were at the level of steady tendecy $RR_{\text{ппж}\geq 1,75}=2.22$ (95% CI=0.84 ÷ 5.83; 90% CI=1.00 ÷ 4.99). It is noteworthy that the critical cutoff points of all indicators of the lipid profile lay in the range of reference values.
Conclusion
For T2DM screening, a Findrisc survey is justified, in spite of normal lipid profile values, ultrasonography of adipose tissue is required.

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EP259

Personalized approach to the management of T2DM: Sibutramine+dapagliflozin – synergism at the start clinical case

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Patient C., b. 1962 went to the clinic to a urologist with complaints of painful, rapid urination, dry mouth, thirst, a constant feeling of hunger in the daytime. A biochemical blood glucose(bg) level of 10.4 on an empty stomach. At the initial examination by an endocrinologist, bg at a reception of –8.0 mM/l on an empty stomach. BP-134/78 Ps-78. Height-178 Weight-101.5 BMI-32.0. HbA1c-7.4% basal insulin(bi)-28.3 (3.0–25.0) stimulated insulin(si)-56 (3.0–25.0). Basal C-peptide-4.8 (0.8–5.1). Stimulated C-peptide-7.1 (0.8–5.1). Leptin-28.0 (3.7–11.3). The diagnosis was made: T2DM with a target level of HbA1c of less than 6.5%.

Background

Obesity 1 Recommended: Dapagliflozin 10 mg Sibutramine 10 mg. After 21 days bg intake 6.4 2 hours after breakfast. GP: 5.1–4.5-5.4–5.8. Weight-93.5 (–2.5 per week) and –8.0 for the entire observation period – 3 weeks. After 30 days bi 8.3 (3.0–25.0), si 16 (3.0–25.0). Basal C-peptide-1.8 (0.8–5.1). Stimulated C-peptide-2.1(0.8–5.1) Leptin-8.0(3.7–11.3) bg at the reception is 5.5 mM/l 2 hours after breakfast. GP: 5.3–5.9–6.6–5.5 mM/l. Weight-90.0 (–11.5) per month –3.5 kg per 1 week. After 2.5 months from the start of therapy: bg at the reception – 4.3 on an empty stomach. GP: 4.1–5.2–5.3–6.1. BP-115/78 Pulse-78. Weight 79 (–11.0 per month and –22.5 for 2 months) bi-5.3 (3.0–25.0) si-7.2 (3.0–25.0). Basal C-peptide-1.1 (0.8–5.1). C-peptide stimulated-1.6 (0.8–5.1). Leptin-5.3 (3.7–11.3). HbA1c-5.7%. Patient canceled dapagliflozin 10 and sibutramine 10. Prescribed sitagliptin 100 daily morning. After 3.5 months from the start of therapy admission bg – 5.4 2 hours after breakfast. Weight-79.5 (+ 0.5) Height-178 BMI-25.09. GP: 4.9–4.6–5.5–4.8. Continued taking sitagliptin 100 mg in the morning. After 6 months from the last dose and 9.5 months from the start of therapy. BG 5.3 mM/l 2 hours after breakfast. GP 5.1–5.4–5.7–6.1 mM/l during the day. Weight 79.0 (-0.5 for 6 months) Height-178 BMI-25.01 Insulin-4.5 Leptin-1.2 C-peptide-0.9 HbA1c-5.4% BP-121/77, pulse-78 without taking antihypertensive therapy.

Conclusion

The potentiation of the effect of dapagliflozin and sibutramine at the start of treatment of T2DM contributes to the formation of proper eating behavior, a decrease in the calorie content of the daily diet and, thus, leads to the compensation of carbohydrate metabolism in a shorter time, as a result of compliance with the principle of compliance and influence on the pathophysiological mechanisms of the disease

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EP260

Assessment of diabetes balance in patients on insulin analogues

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Objective

The aim of this study is to assess the balance of diabetes in patients taking insulin analogues based on a recent value for their glycated hemoglobin.

Methods

2915 diabetics were evaluated for the period from March to April 2019 with as inclusion criteria a recent glycated hemoglobin and a duration of insulin treatment analogues of more than one year.

Results

Glycated hemoglobin is lower than 7 in only 8% of cases and greater than 9 in 49% of cases. No significant difference in the balance of diabetes according to the length of treatment with insulin analogues.

Conclusion

It is necessary to analyze the real benefit of insulin analogues in terms of diabetes balance as well as the cost-benefit of these molecules.

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EP261

The possibilities of ultrasound in the diagnosis of latent postinjection lipodystrophies

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Introduction

Condition of injected skin and subcutaneous tissue is assessed by visual inspection and palpation and it has only 10–15% diagnostic value. The standard ultrasonography comparison of symmetrical skin areas is not valuable as they are usually used for injections.

Objective

We examined 143 patients, aged 43.3±3.9 years, with DM duration of 6.5±2.8 years, receiving basal-bolus insulin therapy.

Methods

Ultrasonography was performed for 78 volunteers with uninjected skin and subcutaneous tissue of the lumbar and epigastric regions. We determined correction factors that predict skin thickness at the injection site if insulin weren't administered.

Results

Ratio indices at the injection regions were calculated – the ratio of the dermis thickness of the studied to lumbar region. In the anterolateral shoulder region, normal indices were defined: for epidermis in the range of 0.9–1.0; for dermis – 0.5–0.7. In the anterolateral thigh region: for epidermis – 0.8–1.0; for dermis – 0.5–0.8. In the umbilical region: for epidermis – 0.8–1.0; for dermis – 0.6–0.8. In the upper outer quadrant of the buttock: for epidermis – 0.8–1.0; for dermis – 0.7–0.9. With values decrease, hypotrophic lipoatrophy development is expected. When performing ultrasonography and analyzing the ratios of the epidermis and dermis of the lumbar region to injection sites, changes were detected in every 4 (37 patients), which is 25%. Post-injection hypotrophic lipoatrophy was diagnosed in the umbilical region (49%), in the anterolateral shoulder (24%) and thigh (17%) regions, in the gluteal region (10%).

Conclusion

Using ratio indices during ultrasonography, it is possible to diagnose and treat post-injection lipodystrophies in the earliest time in order to achieve the highest insulin injection bioavailability.

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EP262

Use of betablockers in aging patients with type 2 diabetes: Effects on glycemic control

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Background

Aging patients with type 2 diabetes mellitus have a higher risk of developing hypoglycemia. Many studies show the effect of beta-blockers in hiding hypoglycemia symptoms and therefore the occurrence of a severe hypoglycemia. These agents are commonly used in diabetic patients with coronary heart disease. The aim of this study was to assess whether the use of beta-blockersdeteriorates the glycemic control.

Methods

We conducted a retrospective study involved 101 patients with type 2 diabetes mellitus followed at the National Institute of Nutrition and Food Technology of Tunis. All patients were over 65 years old.

Results

The average age was 70.69±5 years. Sex ratio were four female for one male. The majority of patients(71.1%)had a high blood pressure while 21% had a coronary heart disease. The average HbA1c was 9.55±1.92%. Seventy eight percent were treated with insulin. About a third (30.9%) of patients

was treated with beta-blockers; only 37% of them had at least one episode of hypoglycemia and only 13.3% reached the glycemic control target of less than 8% of glycated haemoglobin(HbA1c) vs 26.8% as a percentage of achieving the glycemic goal in patients not taking beta-blockers.
Conclusion
Our study indicates that the use of beta-blockersmay have a role in worsening the glycemic control, so that many physicians are reluctant to prescribe them to patients with diabetes and hypertension but their use is inevitable type 2 diabetic patientswith coronary heart disease.

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EP263

Managing pregnancy in a diabetic patient with chronic kidney disease at the hemodialysis stage: An unresolved case

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Introduction
Pregnancy in case diabetes complicated by chronic renal failure is characterized by a very high maternal and fetal risk.
Method
We report the case of a patient with diabetes and chronic renal failure at the hemodialysis stage who wishes to lead a pregnancy despite all the risks involved and of which she had been informed beforehand.
Results
This is a 39-year-old patient, with type 1 diabetes for 26 years. Her diabetes is poorly balanced (HbA1C=8.4%), multi complicated, with lasered diabetic retinopathy, diabetic peripheral neuropathy, and chronic renal failure, on hemodialysis for 8 years. The menarche was at the age of 17 years with irregular cycles. She has an obstetric history of 5 spontaneous abortions. The current pregnancy was not scheduled. The preconceptional body mass index (BMI) was 21.7 kg/m². The blood pressure were correct. She had microcytic hypochromic anemia with hemoglobin at 6.7 g/dl, a urinary tract infection and peripheral hyperthyroidism of incidental discovery whose etiological assessment is in progress. The phosphocalcic balance was correct. The glycemic balance in this patient was difficult especially on the day of hemodialysis.
Conclusion
conception in diabetic hemodialysis patients is exceptional and requires multidisciplinary management to be able to carry it through without maternal and fetal complications represented mainly by fetal loss, malformations linked to chronic hyperglycemia and anemia.

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EP264

Hearing complications in diabetes – A clinical case

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Introduction
Malignant or necrotizing external otitis (MEO) is an invasive infection between external auditory canal and skull base. It is more frequent in elderly and in diabetic patients or with compromised immune system. As MEO advance osteomyelitis can developed. It is a severe and potential mortal complication of external otitis (EO).
Clinical Case
78 years old man with history of type2 diabetes (good metabolic control) and right ear external otitis. In May 2019 initiate topic ofloxacin after diagnosis of EO. After 15 days he is admitted in emergency department (ED) with persistent otalgia in spite of treatment and was hospitalized on suspicious of MEO for IV antibiotic treatment. Analytically showed leucocytosis, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein(CRP), glycemia 224 mg/dl and HbA1c 6.4%. Cultural auricular exudate: *staphylococus epidermidis*, only sensible for gentamicin, ciprofloxacin and vancomycin. Computed tomography (CT) revealed right media osteomyelitis that was confirmed by technetium scanning. Started ciprofloxacin iv 400 mg with clinical and analytical improvement and was discharged with oral ciprofloxacin and ofloxacin up to 8 weeks of total treatment. Four months later returns to ER complaining with severe otalgia with retro-auricle irradiation in RE. Right otoscopy with mesotympanic perforation without otorrhea, and painful pre and retro-auricle palpation. He has elevated both ESR and CRP. Skull base osteomyelitis recurrence was admitted, being hospitalized under iv ciprofloxacin 400 mg. Cultural auricular exudate isolated a multi-resistant *Klebsiella pneumoniae spp* only sensible for ertapenem. Antibiotic was adjusted, with clinical and analytical improvement. Gallium citrate scanning evidenced favourable evolution maintaining active inflammation. Patient is clinically improved maintaining follow-up in endocrine and otorhinolaryngology consultation.
Discussion
This case resumes a potential and severe complication present in elderly with diabetes. This group of patients are in major risk of developing this condition because macroangiopathic alterations in ear, increased pH of cerumen and phagocytic dysfunction of leucocytes from diabetes. Metabolic control of diabetes is not a risk factor for developing MEO but it is important for treatment success. Not as frequent as *pseudomonas aeruginosa*, colonization by *klebsiella pneumoniae spp* (8–19%) or commensal bacteria staphylococus epidermidis (4–9%) are described in the literature. Suspicion and alert for this pathology allows for successful diagnosis and opportune treatment.

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EP265

Diabetic gastroparesis as an important comorbidity factor: About a clinical case

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Introduction
Gastroparesis associated with diabetic autonomic neuropathy is an underdiagnosed complication, although relatively common in diabetes. It is more prevalent in type 1 Diabetes Mellitus (DM1) with more than ten years of disease and especially in patients with poor metabolic control.
Clinical case
Female, 37 years old, DM1 with 17 years of evolution with poor metabolic control (HbA1c 9.3%) and several microvascular complications such as proliferative retinopathy with decreased visual acuity and diabetic nephropathy with end-stage renal failure, on hemodialysis for about 9 years (initially with unsuccessful living donor transplant). The patient presents an important intestinal dysautonomic component, characterized by chronic diarrhea of over 6 months and more recently with gastroparesis (2 weeks). Admitted in January 2019 after a right frontoparietal hemorrhagic stroke with mass effect and deviation of the midline, without indication for neurosurgery, resulting in left upper limb plegia, left lower limb paresis and associated left central facial paresis. During hospitalization, food intolerance was observed, with no improvement to the different prokinetic therapy instituted (metoclopramide, domperidone, clebopride, erythromycin and ondansetron), requiring total parenteral feeding. Among the tests carried, the patient was submitted to high digestive endoscopy and abdominal CT without contrast, which did not reveal relevant changes. Only after glycemic control was achieved was it possible to progressively reverse the gastroparesis condition.
Conclusion
Diabetic gastroparesis is a complex disease that is difficult to control, with diagnostic workup hampered by the extensive differential diagnosis, associated with an increased rate of hospitalization that requires a multifaceted approach.

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Endocrine-Related Cancer

EP266

Triple malignancy in a single patient including a medulloblastoma, a papillary thyroid cancer and a gastrointestinal adenocarcinoma: A case report

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Second malignant neoplasm following irradiation is a rare sequelae of primary childhood malignancies. Irradiation is a well-known risk factor for the development of benign and malignant thyroid tumors. Here we present the case of a young woman with medulloblastoma, who later developed thyroid cancer and eventually was also diagnosed with a cholangiocarcinoma.
At the age of 7 the patient presented with headaches, nausea, vomiting, fatigue, somnolence and double vision and was diagnosed with a posterior scala tumor. She underwent suboccipital craniotomy with macroscopic complete removal of the tumor. Pathology confirmed medulloblastoma. This was followed by chemotherapy with intrathecal methotrexate. After chemotherapy she received complete craniospinal irradiation (36 Gy+20 Gy boost). Oncologic follow up did not reveal recurrence of medulloblastoma. Endocrinologic workup revealed GH deficiency, but no other pituitary hormone deficiency. GH therapy was not recommended since her history of malignant tumor. At the age of 15 she presented with neck lymphadenopathy and was found to have papillary thyroid cancer. She underwent total thyroidectomy and radioiodine therapy in 4 sessions with a cumulative dose of 800 MBq. Regular endocrinologic follow up with tumor markers and imaging did not reveal evidence of thyroid carcinoma recurrence. At the age of 27 she became pregnant. Her early pregnancy was complicated by gestational diabetes as well as an ovarian cyst, for which she underwent exploration laparotomy and left adnexectomy while 23 weeks pregnant. In the 37th week of her pregnancy during a routine endocrinology appointment she was found to have icterus, therefore urgent C-section was recommended. Since the icterus did not resolve after the delivery she had an ERCP and a biliary stent was placed. MRCP showed an intrahepatic tumor. Initial biopsy showed adenocarcinoma with an unknown pancreatic vs gastric vs biliary source. She had a percutan transhepatic drain placed. Subsequent exploratory laparotomy showed peritoneal carcinosis and biopsy revealed cholangiocarcinoma. Due to the extent of her disease surgical treatment was not possible, but palliative chemotherapy was planned. This had to be postponed due to bilateral pulmonary emboli. In the interim her disease has further progressed and she unfortunately passed away before she could have started her treatment.
While having thyroid cancer after irradiation for medulloblastoma could be accounted for the irradiation itself, the development of this patient's third tumor raises the possibility of a genetic abnormality leading to development of multiple tumors. We are currently conducting genetic testing to further investigate this possibility.

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EP267

Raised Metanephrines in SDHB mutation- the hunt for the source

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We present a case of a 24 year old lady with known SDHB mutation. She was referred from the genetics clinic in view of a strong family history of premature paraganglioma at the age of 17. On initial clinic assessment she exhibits no symptoms suggestive of paraganglioma or pheochromocytoma. Her blood pressure is normal at 120/75. pulse of 60–80bpm. Physical examination was unremarkable Her Plasma normetanephrine done on two separate occasion were elevated at 1600 pmol/l and 2157.5 pmol/l (upper limit 1180) urine normetanephrine 5.7 umol/24 hours (upper limit 3), raised urine metanephrine at 6.4 umol/24 hrs. Her 123I-MIBG scan 1 year ago showed physiological distribution in the salivary glands, liver, supra renal regions and bowel with excreted activity in the urinary bladder. SPECT/CT images of the abdomen suggested some enhancement in the left pelvis in but it was felt likely to be normal activity from an ovary given her age. An MRI of the abdomen was normal and octreotide scan show no scintigraphic evidence of avid octreotide disease, tracer uptake was normal. She subsequently presented with urinary symptoms with increased frequency and constant pressure in the bladder. with persistently elevated metanephrines. An ultrasound scan of her pelvis showed an irregular solid highly vascular mass which measures $24 \times 20 \times 21$ mm. A repeat MRI neck, chest abdomen and pelvis found a 24 mm likely paraganglioma exophytic of the left wall of the bladder. Her MRI pituitary gland was normal. She was alpha and beta-blocked prior to surgery. She undergone an open excision and partial cystectomy for her paraganglioma. Her histology findings are consistent with a perivesical paraganglioma with Ki67 proliferation index of (1–2%). Her urinary function has returned to normal and she is due further follow up by the endocrinology team.
Conclusion
Urinary bladder paraganglioma is an unusual tumour arising from chromaffin cells of the sympathetic system of the urinary bladder wall accounting for<0.05% of all bladder neoplasms, often occurs in young female. (1) They are frequently located at the dome or the trigone of the bladder and may be non-functional or functional (2) Mutations in SDHB are the most commonly found gene mutations and are associated with younger ages at presentation, higher rates of metastases and poorer prognosis(1) We highlight the value of pelvic ultrasound in screening and diagnosis of bladder paraganglioma as the sensitivity for detection of familial PHEO and paranganglioma through MIBG scintigraphy is about 53–60.9%.(3)

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EP268

How much time is spent on electronic prescribing in an endocrinology outpatient clinic?

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Introduction
In a US study of general practitioners, 50%-60% of their working time was found to be dedicated to paperwork and electronic medical record-keeping (including electronic prescription – EPC writing)[1].
Aim
Given the mandatory use of EPC in Greece, we wanted to assess the time required for this in the daily practice of our outpatient endocrinology clinic.
Method
In one of the outpatient (OUP) clinics of the Department of Endocrinology, Diabetes and Metabolism of a secondary women's hospital, the time corresponding to EPC was compared to the time spent in the OUP (regarding history taking, clinical examination & laboratory results' assessment). At the daytime OUP clinic, four specialists and three fellows, all with>5 years of EPC experience, examine all regular and emergency cases (there are no personal appointments). In the OUP, EPC is handled exclusively by physicians who take care of the individuals examined. The Webtime Tracker application was used to estimate EPC time, while the time required for EPC in days of general and gestational endocrinology (GE+G) clinics was compared to time spent on EPC in days of type 1 & 2 diabetes patients clinics (GE+D). Differences in EPC time were assessed by the Kruskal Wallis (KW) test, setting the statistical significance at the level of 0.05.
Results
In 101 man-hours of an OUP clinic (GE+G: 77 hours and GE+D: 24 hours), 471 subjects were examined (GE+G: 366 and GE+D: 105 subjects, respectively). The percentage of time spent on EPC was 33% overall (Q25–75: 25% –40%). More specifically, the distribution of EPC time was GE+G: 35% (Q25–75: 25% –41%) & GE+D: 32% (Q25–75: 24% –37%), respectively (KW $P>0.1$).
Discussion
A significant proportion of OUP work time was devoted to EPC, without differences on the type of clinic. In health systems, everyone is creating information that produces more bureaucracy, while doctors do not plan much of the latter[2]. Hospital doctors in Greece receive little help to serve bureaucracy and hospitals do not invest in their secretarial and administrative support. If these problems are not addressed, doctors will have less and less time to examine and treat patients.
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EP269

Multiple endocrine neoplasia: A case series of 7 families

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Introduction
Multiple endocrine neoplasia (MEN) is a rare genetic syndrome characterized by occurrence of tumors involving two or more endocrine glands. Four types are described: MEN1, MEN2, MEN3 and the recently identified MEN4. Due to the complexity of the syndromes, it is difficult to manage these patients. Our objective was to describe the clinical features of individuals from 7 families with a diagnosis of MEN1 or MEN2 and identify current challenges in clinical practice.
Case series

1. Female, 48, presented with appendicitis at the age of 40. Pathology reported a neuroendocrine tumor (NET). Later, she was diagnosed with primary hyperparathyroidism (PH) and pituitary adenoma. The diagnosis of MEN1 was made at 44. Both her children have the mutation.
2. Female, 38, presented with prolactinoma at 18 and was prescribed dopamine agonists. Due to infertility, she was referred to assisted reproductive technology and later was diagnosed with PH and NET. The diagnosis of MEN1 was made at 37.
3. Female, 66, presented with acute pancreatitis at the age of 49. An abdominal MRI revealed nodular lesions of the pancreas. The pathology reported NET. Later, she was diagnosed with PH and pituitary adenoma. The diagnosis of MEN1 was made at 59. She has two children, 1 with the mutation.
4. Female, 50, presented with hypothyroidism. A thyroid ultrasound revealed a large nodule. The cytology reported medullary thyroid carcinoma (MTC). The diagnosis of MEN2 was made at 46. She has five children, 2 with RET mutation. Both underwent prophylactic surgery.
5. Female, 74, presented with goiter and had total thyroidectomy (TT). The cytology reported MTC. The diagnosis of MEN2 was made at 68. She has 3 children and 4 grandchildren with the mutation. One of them, 18 years, rejected prophylactic surgery. All other family members underwent TT.
6. Male, 60, presented with MTC and pheocromocytoma at 40. Genetic testing revealed no RET mutation. He has 3 children.
7. Male, 58, diagnosed with acromegaly at 36 years, had surgery and is treated with somatostatin analogs. At 46, he underwent left nephrectomy for a renal mass. At 48, he presented PH. Genetic testing revealed no MEN1 mutation. Suspicion of MEN4.

Discussion
From our series, the main clinical challenges were:
Pregnancy in MEN1 patients (case 2);
Rejection of a prophylactic surgery (case 5);
Clinical diagnosis and surveillance after a negative genetic screening (cases 6–7).
We reviewed the literature and discuss the management of these patients.

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EP270

All with men 2A in one family?

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Multiple endocrine neoplasya type 2 (MEN-2) is a rare hereditary complex disorder caused by a germline activating mutation of the RET proto-oncogene. The estimated prevalence is approximately 1:30.000. Three clinical forms have been described depending on the phenotype: MEN2A (80%), MEN2B and familial medullary thyroid carcinoma (MTC).
Clinically, MEN2A present with MTC (80–100%), unilateral or bilateral pheocromocytoma (40%) and primary hyperparathyroidism (25%) and ocasionally with cutaneous lichen amyloidosis/Hirschprung disease, within a single patient.
Case report
A 50-year-old male patient, hypertensive and diabetic, was reffered to us with MEN 2 suspicion. He presented in a general hospital with nonspecific symptoms: abdominal and low back pain, loss of appetite, vomitting and weight loss; while his 23-year-old daughter has already been diagnosed in our hospital with MEN2A syndrome with a rare high risk RET mutation (Cys634Tyr). Anterior abdominal CT scans revealed bilateral adrenal masses. Hormonal tests suggested high plasma and urinary metanephrines (MN-1.015 pg/ml, 5.806 mg/24 h) and normetanephrines (NMN-2.545 pg/ml, 7.696 mg/24 h), high cromogranin A(538 pg/ml) confirming pheocromocytoma. Thyroid ultrasound described a non-homogeneous, vascularized right lobe macronodule with calcifications. High levels of calcitonin(1858 pg/ml) and CEA (75.27 ng/ml) with bilateral pheocromocytoma confirmed MEN2A. The patient underwent bilateral adrenalectomy performed by the team of doctors Paun and Beuran and total thyroidectomy this january. Histopathological exam confirmed bilateral multifocal medullary carcinoma – T2 mNxMo. His family was invited for MEN screening, but his son is refusing and his brother is postponing the investigations. His 27-year-old nephew, with no clinical features, came for investigations. Hormonal test highlighted high plasma and urinary MN(448 pg/ml, 956 mg/24 h) and NMN(504 pg/ml, 760 mg/24 h), high calcitonin (1244 pg/ml) and CEA (42.02 ng/ml) and thyroid ultrasound that showed a left lobe nodule with calcifications. An abdominal CT scan was performed and revelead a right adrenal nodule and left adrenal hyperplasia. Both men's genetic testing highlighted the same high risk RET mutation (Cys634Tyr).
Particularities
An early onset of the syndrome and the presence of an high risk mutation in his family suggest for an highly aggressive phenotype of the syndrome. A notable intra-familial variability in disease aggressiveness was observed because her father presented with late onset of the MEN2A and developed complications.
Conclusions
Simultaneous apparition of bilateral pheocromocytoma and MTC in a patient are mandatory for further investigations and detailed genetic screening to all members of the family. Thus, early diagnosis and regular follow-up can provide a better outcome, but the prognosis in variable.

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Environmental Endocrinology

EP271

Iodine status in the Faroe Islands among adults aged 40–74 years old

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Objective
The aim of this study was to examine the urinary iodine concentrations (UIC) in an adult population in the Faroe Islands. Iodine status in the adult population assumed to be sufficient due to the high frequency of seafood consumption1 although UIC has not been investigated previously in the Faroe Islands. World Health Organization recommends monitoring iodine status in all populations. Iodine nutrition is a key determinant of thyroid disease risk
Design
A population-based cross-sectional survey was conducted in 2011–2012 a sub-group donated a urinary sample. We measured iodine concentrations in 491 participants, 294 men and 197 women aged 40–74 years.
Methods
Urine samples were stored at minus 80 degrees Celsius. Iodine level is determined in microgram/liter (mg/l) by the ceri/arsen method after alkaline ashing.
Results
The median UIC was 101 mg/l (21 to 1870 mg/l). Severe deficiency did not occur in this study group (UIC,<20 mg/l); 10% of the participants were moderate insufficient (UIC<50 mg/l). In total 36% were in the target range (UIC, 100–199 mg/l) but 38% were mild insufficient. Nearly 15% had higher levels than recommended (UIC≥200 mg/l). Smoking habits did not affect the results. There was not significantly differences in age groups as seen in other studies. Overall UIC was significantly higher in males 115 mg/l than females 86 mg/l ($P<0\times001$).

Conclusion
It is important not only that the median iodine intake is sufficient, but also to consider the total iodine exposition in the population. With nearly half, the study population moderate to mild deficient as determined by WHO criteria especially the status in females could be a cause for concern. Health authorities need to form an opinion about and taking a position on Iodization program and regular assessment of iodine nutritional status is needed.

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General Endocrinology

EP272

Effect of pregnenolone derivatives on the selective inhibition of 5α-reductase 2 activity

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Benign prostatic hyperplasia and prostate cancer are androgen-dependent diseases. Dihydrotestosterone (DHT) is a 5α-reduced metabolite of testosterone (T), which is the causative factor for the progression of these diseases. The 5α-reductase enzyme (5α-R) converts T to DHT, which is responsible for increasing cell proliferation, and hence inhibition of this enzyme could lead to potential treatments for these afflictions. This study aimed to determine the biological activity of three series of pregnenolone derivatives as inhibitors of 5α-R. Also, these molecules evaluated as antiandrogens on androgen-dependent glands. The biological activity of these derivatives was determined by the concentration of each one needed to suppress the activity of both 5α-R types 1 and 2 isozymes by 50% (IC_{50}). The effect of these derivatives on the weight of the prostate, seminal vesicles, and diameter of the flank organs of castrated hamsters previously dosed with 1 mg/Kg T was also established. *In vitro* experiments showed that derivatives **1f**, **2b**, and **3d** were very effective inhibitors of the activity of 5α-R2, showing IC_{50} values of 21.8, 20, and 15 nM, respectively. However, derivatives **2b** and **3b** showed a lower inhibition effect on 5α-R1. The data also indicated that derivatives **2b**, **1f**, **3b**, and **3d** were very active in reducing prostate weight in the hamster model of benign prostatic hyperplasia as well as seminal vesicle weight and the diameter size of the pigmented spot of flank organs. Therefore, pregnenolone derivatives studied suppressed type 2 5α-reductase activity, and because of this, the weight and dimension of androgen-dependent organs decreased.

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Testosterone modulates the corticotropin releasing hormone-induced pro-oxidant activity in macroendothelial cells

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Introduction
Limited data, support the notion that testosterone induces oxidative stress. Corticotropin-releasing hormone (CRH) participates locally in the endothelial inflammatory response by regulating the pro-oxidative mechanisms of the endothelium, inducing its adaptation to local stress. The present study was undertaken to determine whether the CRH induced pro-oxidant activity in macroendothelial cells under basal conditions, is regulated *In vitro* by androgen (testosterone-DHT).
Materials and methods
EA.hy926 endothelial cells were cultured in DMEM phenol red free without FBS for 24 hours. Growth medium was replaced and then CRH (10^{-7} M), and CRH plus testosterone (0.5nM) or DHT (0.5nM) alone or in combination with the androgen receptor antagonist flutamide (50nM), were added to the culture media and cells incubated for 2 more hours. Intracellular reactive oxygen species (ROS) content, endothelial nitric oxide synthase (eNOS) activity, nitric oxide (NO) levels, superoxide dismutase (SOD) activity, catalase activity (CAT), and glutathione (GSH) levels were measured.
Results
Testosterone and DHT abolished the CRH-dependent decrease of eNOS ($P<0.001$ vs CRH) and NO ($P<0.001$ vs CRH), as well as the increase of catalase activity ($P<0.001$ vs CRH). Moreover, both androgen amplified the CRH-dependent increase of oxidative burden ($P<0.001$ vs CRH) and SOD activity ($P<0.05$ vs CRH). All the above effects of androgens were abolished by flutamide suggesting action through the androgen receptor. Finally, testosterone and DHT had no significant effect on cellular GSH levels and the GSH/GSH+GSSH ratio in EA.hy926 cells.
Conclusion
Our findings indicate that in endothelial cells, *In vitro*, testosterone and DHT modulate the pro-oxidant effect of CRH, by relieving its inhibitory effect on eNOS and NO release and exacerbating its stimulatory effect on intracellular ROS levels as well as the SOD activity levels while restoring its stimulatory effect on catalase activity.

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EP274

Poor lifestyle as a risk factor for endocrine pathology among medical students

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Medical students around the globe undergo serious amounts of stress related to adjustment to the rigors of medical curriculum, to change of roles, and other factors intrinsic to medical education. Research has shown that stress among medical students is associated with generally lower academic performance and lower job satisfaction once physicians. The goal of this study was to analyze the influence of healthy lifestyle practices not only on medical students' health overall, but specifically on prevalence of endocrine pathology among medical students. 235 medical students from 11 countries participated in the study. Students were both those who studied in native languages to those countries and those enrolled in English language programs. Overall, over 20 cultural and ethnic back-grounds were represented. Medical students were asked to self-report their lifestyle practices (diet, exercise, alcohol and tobacco use, sleep quality, level of stress), occurrences of endocrine disorders, and academic performance in medical school. The following standardized peer-reviewed assessment instruments were used: Simple Lifestyle Indicator Questionnaire (SLIQ), Brief Insomnia Questionnaire (BIQ), questions regarding general overall academic performance, as well as performance on standardized tests (USMLE-like) during medical school. While prevalence of endocrine disorders generally is around 5–6%, in our sample 12% of medical students experienced some form of endocrine pathologies. Students seemed to have overall higher scores on the Exercise subscale of SLIQ than on the Diet subscale, which implied that these medical students' diets are generally worse than their exercise habits. Medical students' stress and sleep scores exhibited a negative, medium-strength correlation, suggesting that that lack of sleep and higher reported stress levels are associated. On average, students with endocrine pathology reported higher academic overall performance and higher licensing exams test scores. Medical students' SLIQ and BIQ scores inversely correlated, which suggested that poorer lifestyle choices were associated with greater insomnia.

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Endocrinopathy in patients with glomerulonephritis undergoing renal biopsy – single center observation

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Introduction
Endocrine disorders and kidney diseases can coexist. Some of these have a common pathophysiological background. Strategies for treating endocrinopathy or glomerulonephritis (GN) may affect the function of the endocrine system and kidney.
Aim
The study was aimed to assess the correlation of kidney biopsy results performed in people with suspected GN with thyroid function, metabolic syndrome and diabetes occurrence.
Material and methods
The research consisted of retrospective analysis the data of 233 (79.8% women) patients, the age range of the group was 7–79 (44.5±17.4), hospitalized in our clinic from 2013 to 2019 (75 months) who underwent renal biopsy due to suspected GN.
Results
The most common indications for renal biopsy were: nephrotic syndrome (n=84; 36%), no nephrotic proteinuria (n=24; 10.3%), worsening renal function (n=91; 39.1%), nephritic syndrome (n=34; 14.6%). Membranous glomerulonephritis (n=33; 14%), rapidly progressive glomerulonephritis with extra capillary crescents (n=21; 9%) and focal segmental glomerulosclerosis (n=21; 9%) was the most common histological diagnosis observed in kidney biopsies. Our analysis proved higher occurrence of thyroid dysfunction: hypothyroidism (n=29; 12.4%), low FT3 syndrome (n=30; 13.1%), subclinical hypothyroidism (25; 10.7%). Diabetes coexisted in 32 (13.73%) patients, whereas diabetic nephropathy (DN) was found in renal biopsy only in 6 (2.57%) patients. Many patients had steroid-induced diabetes (14%). There wasn't higher occurrence of obesity (27.1%) and overweight (24.9%). Arterial hypertension coexisted in 108 (46.3%) patients.
Conclusions
Additional diagnosis for thyroid pathology is worth to be considered in monitoring patients with GN. A small percentage of diabetics had features of DN in kidney biopsy. There was no higher occurrence of obesity and overweight in the population with GN.

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EP276

Aging, depression and movement

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Old people will have to take care of themselves as long as possible. The challenge for the future is therefore not to extend human age at all costs, but to extend human self-sufficiency. Two years ago, we showed that patients with anxiety and affective disorders ('depression') felt great after a month's stay at the spa, improved in a number of endocrinologic parameters. In this work we try to explain the physiological changes of stay in a spa without pharmaceuticals or medicinal waters, without peloids (peat) 'only' climatotherapy and kinesiotherapy (movement). To some extent, the characteristics of aging are common to depression. In old age, the production of hormones such as serotonin (5-hydroxytryptamine) and melatonin (5-methoxy-N-acetyltryptamine) decreased. Important is the oxygenation of the body movement especially in healthy air, a varied diet rich in amino acids. Aging is often accompanied by loss of muscle mass – sarcopenia. No pharmacological or behavioral intervention targeting sarcopenia has been shown to be as effective as exercise. The state of mind and the emotional (limbic) system also have an impact. High blood pressure and thus cardiovascular disorders may also be caused by the formation of autonomous aldosterone-producing clusters, which were recently proven. Aerobic exercise: preferably a quick walk leads to the maintenance of baroreflex, muscle mass adjustment and thus to the strength of an aging individual. The explanation lies in function of the limbic system: control of anxiety and fear, control of social and emotional; behaviour; participation in short-term memory processes; cardiac and respiratory control (connection to the hypothalamus); secretion of endocrine glands. The hypothalamus through the limbic system (of which it is an integral part) affects movement and backwards. It connects the olfactory stimulus, eye perception, auditory perception, skin perception during movement, all information from the equilibrium and basal ganglia and movement planning (cortex, prefrontal and frontal cortex). In conclusion, it can be said that for aging people, matters the same as to patients who have undergone spa treatment. Persons who often and even moderately move in healthy air and who follow regime measures i.e.: sleep and diet rich in vitamins – hope that the positive changes that have occurred in his organism could persist for many weeks or months, long-term stabilizing and anti-progressively in terms of healthy aging.

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EP277

Glioma of the optic pathways revealed by a nystagmus

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Abstract
Gliomas of the optic pathways are rare tumors that are mainly seen in children. We report the case of a 4 year old boy followed since the age of 6 months for a nystagmus. It is a boy born at term by vaginal way resulting from parents not consanguineous, the parents noted the nystagmus when their child was 6 months old. After opinion of the ophthalmologist, the child is treated only by optical correction, it is only at the age of 4 years following the installation of headache that a brain MRI is performed revealing a tissue damage process expansive solido cystique, supra sellaire developed at the expense of the chiasma, the cystic portion of which is posterior and the anterior solid portion measuring 31 × 38 × 36.6 mm. The child was referred to neurosurgery for treatment and then referred to our service. The ophthalmological examination finds a nystagmus without strabismus or exophthalmos. Visual acuity could not be appreciated given the age of the child. Examination of the fundus revealed a bilateral sectoral optic atrophy. The somatic examination did not find café au lait spots or other lesions that could suggest neurofibromatosis. The neurological examination is normal, in particular no intracranial hypertension syndrome. Endocrine examination is without abnormalities.
Discussion
Tumors of the optic pathways are dominated by glioma and then meningiomas. Gliomas are the most common brain tumors in children and adolescents, boys are affected twice as often as girls. These tumors include forms of very good prognosis such as pilocytic astrocytoma, and types much more difficult to treat such as infiltrating glioma of the brainstem. Low-grade (benign) gliomas are more common in younger people, while malignant gliomas affect older children or adolescents. The decrease in visual acuity is the first sign of ophthalmological appeal, however the decrease in visual acuity may go unnoticed in young children in whom the tumor may be revealed by nystagmus or strabismus.
Conclusion
The therapeutic management of gliomas of the optic pathways goes from simple clinical and radiological monitoring, to surgical treatment or chemotherapy or radiotherapy.

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Physicians' attitudes towards pharmaceutical promotion: Investigation in endocrinology

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Recently, special attention has been paid to the relationship between doctors and the pharmaceutical industry. The aim of this work was to evaluate the attitude of Tunisian endocrinologists towards pharmaceutical promotion.
Methods
It was a cross-sectional study based on an anonymous 9-item survey about the attitudes and behaviors of physicians towards the pharmaceutical promotion. The study included 120 participants.

Results
One-third (34.2%) of the physicians didn't complete the survey. We analyzed the responses of 75 participants: 32 residents and 43 specialists. The inexpensive gifts were appreciated by the majority of participants. Costly gifts were judged less frequently appropriate, especially by specialists ($P<0.001$). However, these expensive gifts were received or desired by many participants, and significantly more by residents than specialists. Among residents, 9.4% and 15.6% thought that respectively their prescriptions and those of their colleagues would be highly influenced by promotion ($P=$ns). This difference was significant among the specialists: respectively 4.7% and 35.3% ($P=0.002$). Training about conflict of interest is inadequate or non-existent according to 96.8% of residents and 97.6% of specialists ($P=$ns). Contact between learners and medical visitors was to be prohibited based on 9.4% of residents and 36.6% of specialists ($P=0.007$).
Conclusions
The majority of participants confirmed that they received or wanted to receive gifts from the pharmaceutical industry, but they said that this did not affect their prescriptions. Literature shows that gifts, however small, are very effective in subtly changing the therapeutic attitudes of physicians. Awareness is needed to ensure an independent medical prescription in our hospitals.

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EP279

Myasthenia gravis during anti PD-1 therapy

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A 66-year-old patient was diagnosed with lung cancer. In the interview, smoking for 40 years, about 20 cigarettes/day. Due to the intensifying cough, an x-ray of the chest was performed, a large tumor (12 cm) of the mediastinum and the right cavity was found. In the histopathological examination squamous cell carcinoma. Stage T4 N2 M0. Due to tumor inoperability, the patient was qualified for sequential chemo-radiotherapy. He received 3 cycles of chemotherapy (navelbin and cisplatin). After the chemotherapy, the lesion decreased to 6 cm, but it still infiltrated the division of the right and intermediate bronchi, and was still adjacent to the division of the right pulmonary artery and superior vena cava. Radiotherapy was used, however, in the control chest CT the dissemination of the disease was described: new changes appeared in the right lung apex up to 2.5 cm. In view of the progression of the disease, it was decided to take another type of treatment. The patient was referred to a center where immunotherapy is used. The histopathological block was examined again, immunological tests were performed. Tumor receptors have been shown to be present. The patient was qualified for anti-PD1 immunotherapy. Drug treatment brought excellent results. The lesion significantly decreased, peripheral lesions in the right lung disappeared. However, autoimmune hypothyroidism has emerged and requires levothyroxine therapy. Adrenal function remained normal. Treatment tolerance was very good. After a year of using immunotherapy, there was a significant weakness and decrease in muscle strength. The patient left home only for short walks, even clothing caused significant fatigue. It was difficult for the patient to raise their arms. Shortness of breath appeared, breathing air into the lungs was a big effort. The reason for the weakness was not adrenal insufficiency or pneumonia. Myasthenia gravis was suspected because of eyelid drooping and speech silence. Anti-acetylcholinesterase antibodies were determined. Their presence confirmed the diagnosis of myasthenia gravis. Pyridostigmine (acetylcholinesterase inhibitor) therapy was initiated. No ANA antinuclear antibodies or myositis panel antibodies were detected. Significant improvement in the patient's condition was achieved after initiating pyridostigmine treatment. The drug was used in a dose of 60 mg every 4 hours. The patient is in a very good general condition, he is continuing immunotherapy.

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Pituitary and Neuroendocrinology

EP280

Rare occurence of two metachronous bladder tumours, of which one is neuroendocrine

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Introduction
Neuroendocrine tumors (NETs) are rare tumors that originate in cells from the neural crest, widely distributed in the body. Genitourinary (GU) NETs occurring in the bladder represent less than 1% of these primary malignancies. We present the case of a patient with two metachronous bladder tumors, of which one is NET.
Case report
Male patient, 52–year-old, ex–smoker, known with hypertension, dyslipidemia and benign prostatic hyperplasia came to our clinic following the diagnosis of a neuroendocrine tumour of the bladder. Three years prior to presentation, after gross hematuria, transurethral resection of a bladder tumor (TURB) was performed. The histopathological examination revealed urothelial carcinoma of high grade (G3) infiltrating the lamina propria, with patterns of glandular differentiation; no invasion in the muscularis propria. After surgery, the patient developed left orchitis. 10 months later, imaging follow-up identified a second bladder tumor for which TURB was performed again. The histopathological examination revealed small cell neuroendocrine carcinoma (SCC) with immunoreaction positive for synaptophysin, chromogranin and p16 and a Ki-67 index of 95%. The patient refused radical cystectomy and underwent 4 cycles of Cisplatin and Etoposide combination chemotherapy, well tolerated. Whole body positron emission tomography was negative – the investigation was, however, inconclusive, because of the physiological urinary elimination of radiopharmaceutical. Native computed tomography of the thorax and abdomen and contrast-enhanced magnetic resonance imaging of the pelvis confirmed the absence of recurrent or metastatic disease. No preoperative neuroendocrine tumour markers values are available, but following the second surgery, serum chromogranin A, serotonin, neuron-specific enolase and urinary *5*-hydroxyindoleacetic acid are within reference range. Ecocardiography showed hypertensive cardiomyopathy. The patient denies *symptoms* of carcinoid syndrome.
Conclusion
GU NETs are very rare and usually affect women. Moreover, male GU NETs commonly involve the prostate. Last, but not least, SCC is an aggressive neoplasm that usually occurs at advanced stages, in senior population (male: female ~ 3:1) and, in approximatively 50% of cases, it is mixed with urothelial carcinoma, adenocarcinoma, squamous cell carcinoma, and/or may have sarcomatoid features. Thus, the only features in accordance with the literature are the patient's gender, history of cigarette smoking and no association with paraneoplastic syndromes. In conclusion, bladder SCC is a rare tumour whose generally poor prognosis was much improved in this case by diagnosis and treatment in the presymptomatic and presecretory stage. The peculiarity of the case further consists of the high Ki-67 index (95%) and history of urothelial carcinoma.

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EP281

Inspection of the internal jugular vein pulse appears to be superior to impedance analysis for determination of volemia in a Hyponatremia outpatient clinic

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Measurement of electrical impedance has been proposed as a way to determine whether a hyponatremic patient is hypovolemic or euvolemic. We compare the usefulness of the physical examination (PE) with bioimpedance for determination of volemia in an outpatient hyponatremia clinic.

Method
Descriptive prospective analysis. 11 patients attended at the hyponatremia clinic of a tertiary hospital were evaluated. Impedance was measured by a SECA, indicating the percent of weight corresponding to body water. Furthermore, by applying internal algorithms, SECA indicates whether total body water (TBW) and extracellular body water (EBW) are normal, increased, or reduced in a given patient, based on body composition, gender and age. Results were compared with 'gold standard' evaluation of volemia by inspection of the maximum height of the internal jugular vein pulse (PE). Patients were considered euvolemic if the pulse was 1–3 cm above the sternal angle when reclined, and hypovolemic if found below the sternal angle.
Results
2/11(18%) women. Median age: 72 [IQR 14]. Four patients were hypovolemic by PE. In 3/4, TBW was found to be low by SECA. However, impedance found low EBW in only 1 patient. In fact, in 1 patient SECA analysis found ECW to be elevated. Based on PE, in 2 patients the tolvaptan dose was reduced, in another 2 fluid intake was increased. In all 4, clinical and analytical improvement ensued. In 3 patients who were euvolemic by PE, with serum sodium ≤ 135 mmol/l, SECA found TBW to be low, normal, or high, with corresponding ECBW low, high, and high respectively. Patients were told to reduce fluid intake. All had improved at follow-up. Four patients were eunatremic, and euvolemic by PE. SECA indicated low TBW in one, normal in 3. EBW was normal in 3, and upper limits in 1. Patient therapy was not modified. Patients were well at follow-up. SECA's findings of TBW diverged from its observed EBW in 6/11 patients. SECA's TBW report coincided with the PE in 7/11 cases, whereas SECA's EBW report coincided with the PE in 6/11.
Conclusion
In a Hyponatremia clinic, physical examination of the internal jugular pulse, directly indicating volemia, provides a better tool for clinical decision-making than impedance measurement. Furthermore, given that water diffuses freely between body compartments, SECA's discrepancy as regards total and extracellular body water is surprising. SECA impedance analysis appears to be of limited value in an outpatient setting for determination of volemia.

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EP282

Pituitary metastasis as a rare cause of diabetes insipidus

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Introduction
The most common cause of diabetes insipidus is idiopathic. In some rare cases, it can be secondary to metastasis to hypothalamic–pituitary region.
Case report
We report a case of 68-years-old female patient presented to our clinic with complaints of polyuria and polydipsia. She had medical history of breast adenocarcinoma 6 years ago treated with surgery, neoadjuvant radiotherapy and 8 cycles of chimiotherapy. On physical examination she had no notable pathological findings and the evaluation of daily urine volume was at 12 l/day. Laboratory data showed normal glucose and calcium level with plasma osmolality calculated 301 mosm/kg and hypotonic urine (Urine osmolality = 90 mos/kg). Water deprivation test revealed central diabetes insipidus and desmopressin therapy was started. After the therapy complaints of polyuria and polydipsia disappeared. MRI of the brain showed infiltration of the pituitary stalk compatible with metastases and absence of posterior pituitary bright spot. Further investigation showed multiple pulmonary and hepatic metastasis and the patient was referred to the medical oncology department.
Conclusion
Tumor metastasis to the pituitary gland is a rare condition that should be noted in a cancer patient with diabetes insipidus. A better understanding of its clinical manifestations could lead to earlier diagnosis, appropriate therapy and potentially improving quality of life.

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EP283

Severe hypoglycemia in diabetic patient with long lasting undiagnosed empty sella syndrome

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A 45 year old female was referred to the Endocrinology department with complains of severe fatigue and weakness from basic daily activities, also irregular menstrual circle during last five years. Twelve years back she had twin pregnancy, premature delivery on 29th week, and absence of lactation. Afterwards she gradually lost 6 kg of her body weight and her menstrual circle become sparse and disappeared five years back. 1.5 years ago type 1 diabetes was diagnosed (C-peptide below range, anti-insulin antibodies elevated), and patient immediately started intensified insulin therapy scheme. Despite of adequate diabetes education she regularly experienced hypoglycemic episodes even from very low insulin doses (2–3 IU of long acting insulin, 1–2 IU of short acting insulin) and was repeatedly hospitalized with hypoglycemic coma. Due fear of hypoglycemia patient rather preferred to skip injections and her last HbA1c was elevated (75 mmol/mol, 9%). Endocrine function tests revealed disturbed pituitary function: plasma TSH was within the normal range (2.5 uIU/ml) despite of markedly decreased FT4 (0.4 ng/ml) and elevated TPO antibodies; her morning plasma cortisol was decreased (0.54 mg/dl), yet ACTH was relatively low (6.84 pg/ml); plasma LH, FSH, estradiol, progesterone, testosterone levels were decreased. MRI scan revealed pituitary gland to be thinned out to less then 1 mm in size. Substitution therapy was immediately started with levothyroxine and hydrocortisone, which led to complete disappearance of hypoglycemic episodes. Within half a year patient regained 6 kg, her BMI become optimal. Her mental and bodily strength returned and she started to menstruate again.
Discussion
We demonstrate the case of female patient having hypopituitarism due to empty sella syndrome, coexisting with autoimmune thyroiditis and type 1. diabetes mellitus. However, it was difficult to determine the primary cause of hypopituitarism. Differential diagnosis in this case is between Sheehan syndrome, lymphocytic hypophysitis or combination of both. In conclusion, our case report is showing importance of testing of pituitary function within the endocrinology setting for unclear severe hypoglycemia in diabetic patients complaining of increasing fatigue and weight loss.

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EP284

Secondary amenorrhea and large uterine myomas in a patient with acromegaly

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Menstrual irregularity is common in women with acromegaly, occurring in 40–84% of patients. Its pathogenesis is still not well established although it is usually attributed to prolactin excess and/or gonadotropin deficiency. Also, since the presence of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) receptors is demonstrated in the myometrium, a pathogenetic role of GH in the development of myoma is examined through different studies. Moreover, some of them particularly emphasise increased risk of developing neoplasms in patients who had been untreated for a long period of time, pointing out the significance of an early diagnosis. A 40-year-old female underwent endocrine assessment for hypertensive paroxysms characterised with sudden rise in blood pressure, up to 190/120 mmHg, over the past 4 years despite the treatment with ACE inhibitor and calcium channel blocking agent. She also reported headaches, deepening of her voice, change in facial features, enlargement of hands and feet (shoe size increased in one number) and secondary amenorrhea. Family history was positive for carcinoma and heart disease. On physical examination, typical acromegalic features were present. Hormonal examination revealed IGF-1 554 ng/ml (58.2–219 ng/ml), IGFBP3 8.23 mg/ml (3.3–6.6 mg/ml), luteinizing hormone (LH) 8.23 mIU/l, follicle-stimulating hormone (FSH) 4.38 mIU/l, estradiol 90 pg/ml, testosterone 1.42 nmol/l along with a modest increase in serum prolactin level (999.74 mIU/l). Thyroid hormones, cortisol and PTH were all in reference range. Pituitary magnetic resonance imaging (PMRI) showed a macroadenoma 21 × 17 × 18 mm with extrasellar extension into the suprasellar region. Further examination showed two large uterine myomas measuring

88 mm and 64 × 56 mm respectively. The patient underwent transsphenoidal surgery and patohistology was consistent with plurihormonal somatotrophic adenoma (GH, prolactin, TSH). After surgery, Hydrocortisone supplementation was started. On six months follow-up, control PMRI demonstrated residual tumour 18 × 8 mm, GH 0.2...0.9 ng/ml, IGF-1 157 ng/ml, IGFBP3 4.80 mg/ml, LH 5.01 mIU/l, FSH 5.59 mIU/l, prolactin 92.74 mIU/l. Amenorrhea is still present along with occasional rises in blood pressure. The patient refuses a proposed surgical treatment of uterine myomas. Concerning patient`s current clinical status, the use of somatostatin analogue is beeing considered due to its effects on tumour rest and proposed role in a reduction in uterine and myoma volume. Menstrual abnormalities should be expected in woman with acromegaly. Therefore, all of them should undergo periodic screening for endometrial neoplastic lesions.

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EP285

Acromegaly and glucose metabolism – A case report

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Acromegaly is a rare disorder caused by growth hormone (GH) and insulin-like growth factor I (IGF-I) overproduction, associated with increased morbidity and mortality. It has different complications, among which insulin resistance, prediabetes and diabetes mellitus are substantial. GH affects glucose metabolism through different mechanisms. The therapy of GH overproduction (for example surgical or radiotherapy) improves glucose metabolism, while different types of medical therapy may worsen it. We present the medical history of an acromegalic patient, diagnosed at the age of 30 years. Although his GH-producing giant adenoma had been operated twice, only partial resection was achieved with intra- and suprasellar tumour remnant. He was initially treated with dopamine agonist, followed by a high dose of first-generation somatostatin receptor ligand (SRL) octreotide LAR. In the meantime, he developed type 2 diabetes mellitus. Since the acromegaly was still active, the therapy was changed to the GH receptor antagonist pegvisomant. Despite its high dose, we couldn't achieve biochemical control. Once the second generation SRL pasireotid LAR was available, ha was given 60 mg monthly, which improved his IGF-I levels, but worsened the glycaemic control. Because of tumour concern and impaired glucose metabolism, the acromegaly is now controlled by a pasireotide LAR and pegvisomant combination therapy. His diabetes is treated with insulin, metformin, SGLT2 inhibitor and a GLP-1 receptor agonist. An overproduction of the contra-insulin GH worsens glucose metabolism. Therefore, lowering pathologically high GH levels by surgery, medical or radiotherapy improves glucose homeostasis. On the other hand, first generation SRLs might worsen glucose metabolism, while second generation SRL pasireotide causes hyperglycaemia in the majority of cases. The optimal therapy for acromegalic patients should be individually taking into account different aspects of the disease.

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EP286

Macroprolactinoma in an adolescent girl with secondary amenorrhea – A case report

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Introduction
Prolactinomas are rarely found in adolescents under 15 (incidence 0.1/1.000.000). They account for 50% of all types of pituitary adenomas in childhood and adolescence (2% of intracranial tumors). The mean time from onset of symptoms to diagnosis is 2.4 years on average for girls. In cases of macroadenomas, TSH and GH deficiency may coexist. The gold standard primary therapy is dopamine agonists. In case of non-response, or the presence of large prolactinomas with compressive effects mainly in the optic chiasm, surgical treatment is recommended.

Case presentation
A14$^{+2/12}$ year-old adolescent girl (weight: 67.6 kg, height: 1.57 m, BMI: 27.4 kg/m^2), was referred for secondary amenorrhea. On physical examination, she was at Tanner stage 3–4 for both pubic hair and breast development. She had facial acne and reported occipital neuralgia. Initial laboratory results showed serum PRL at 705.4 ng/ml (normal: 4.79–23.3 ng/ml). MRI revealed a pituitary macroadenoma (16 × 13 × 15 mm) in the right pituitary lobe that encircled the right carotid artery in the cavernous sinus, while slightly pushing to the left the rest of the gland, without suprasellar projection. The visual fields examination was normal. The patient was initially started on cabergoline 0.5 mg twice weekly and gradually titrated up to 0.75 mg twice weekly, leading to menstrual cycle reappearance. Due to continuous presence of marginally high morning cortisol blood levels at 691.5 nmol/l (normal: 171–536 nmol/l), the HPA axis was assessed with overnight dexamethasone suppression test, low dose dexamethasone test and 24 h urine cortisol levels. The results were within normal limits. Fifteen months later, an MRI revealed that the macroadenoma had degenerated and significantly decreased in size (10 × 11 × 14 mm), while the remaining gland was no longer deviated to the left, nor was the internal carotid artery significantly encircled. Prolactin levels were at 43.1 ng/ml.
Conclusion
Prolactinomas are rarely found in adolescents under 15 years of age. For early diagnosis and treatment, it is very important to assess pituitary gland function in adolescent girls with menstrual disorders or amenorrhea, especially when combined with headache or vision disorders.

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EP287

Obesity in endocrine connections- a finding of nonfunctional pituitary macroadenoma

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Introduction
Spacious sellar area predisposes to late diagnosis of nonfunctional pituitary adenomas and in males even the functional ones such as prolactinomas. Rising prevalence of obesity is mainly associated with sedentary lifestyle and excess of food intake. Only in rare cases has endocrine etiology such as Cushing disease, hypothyroidism or hypothalamic disorders.
Case-report
A 29-year-old man was admitted to our hospital for chest pain, with a highly elevated cardiovascular troponin marker. Acute coronary syndrome was excluded on echocardiography and CT coronarography and he was treated for acute perimyocarditis. Under these stress conditions random thyroid hormones were measured: TSH 1.9 mIU/l [0.35–4.9], fT3 2.5 pmol/l [2.9–4.9], fT4 6.8 pmol/l [9–19], antithyroid antibodies negative and endocrinological follow-up was recommended. Regarding patient's history – obesity since adolescence, currently BMI 38 kg/m^2, otherwise healthy. New findings covered the metabolic syndrome including dyslipidemia, arterial hypertension, and hyperuricemia. Laboratory findings after a month confirmed hypothyroidism of central etiology. Thyroid ultrasound was normal. The whole pituitary hormonal profile was screened, even though the patient was asymptomatic. Central hypogonadotropic hypogonadism and slight hyperprolactinemia were detected (LH 1.3 IU/l [1.7–3.6], FSH 1.7 IU/l [1.5–12.4], total testosterone 2 nmol/l [8.6–29], prolactin 30 mg/l [4–15]). Evident hypo- or hypercortisolism was not present (morning cortisol 298 nmol/l [166–507], ACTH 38.7 pmol/l [1.6–13.9], urinary cortisol 255 nmol/day [100–379]). Growth hormone and age-specific IGF-1 were in norm. Visual fields were intact, but the MRI scan detected sellar expansion (max. diameter 28 mm) with supra- and parasellar progression with an elevation of the optic chiasma. The patient with clinically nonfunctional sellar expansion was referred to neurosurgery for transsphenoidal tumor resection, histologically was confirmed pituitary adenoma with negative immunochemistry of pituitary hormones. Surgery and hormone replacement (currently levothyroxine and hydrocortisone) led to spontaneous BMI reduction to 36 kg/m^2. Testosterone is 4.5 nmol/l and as the patient is planning having a baby, spermiogram is now under investigation and the androgen replacement was postponed.
Conclusion
Nonfunctional pituitary macroadenomas can be found on the basis of diagnosed hypopituitarism, which can evolve slowly. The symptoms of local

compression and expansion and symptoms of partial hypopituitarism appear discreetly and late. In case of obesity and dyslipidemia the evaluation of thyroid function can lead to surprising clinical findings as shows this case report.

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EP288

From visual disturbance to thyroid cancer: An unexpected journey

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A 28-year-old female presented to the optician with visual disturbance, lethargy and headaches, which were initially attributed to long hours of IT work. Despite a trial of eye exercises she experienced worsening colour vision and acuity in the right eye, hence a further consultation with an optometrist. Examination did not reveal a visual field defect. Visual acuity was 6/6 with 9/17 ishihara plates in the right eye and 5/6 with 17/17 ishihara plates in the left. A further referral to the ophthalmologist elicited a history of hearing changes in the right ear. MRI brain revealed a 20 × 28 × 33 mm pituitary mass, requiring an urgent referral to the endocrine team. On review in the endocrine clinic she denied any breast tenderness or galactorrhoea. As part of a general examination (including the neck), deep seated thyroid lobes (clinically not enlarged) with palpable nodules were noted. Pituitary profile showed prolactin 2229 mU/l [normal range (NR) 90–520 mU/l], TSH 0.945 mU/l (NR 0.47–4.68), freeT4 7.1 pmol/l (NR 10.1–30.2) and 9am cortisol < 100 nmol/l. She was commenced initially on cabergoline 0.5milligrams twice weekly and up-titrated to 1.5milligrams twice weekly alongside levothyroxine 100micrograms once daily and hydrocortisone 25 mg daily in divided doses. Repeat prolactin a month later on cabergoline therapy was < 10 mU/l, however pituitary MRI showed no interval change. On further assessment by the neurosurgical team and discussion with the patient, in view of ongoing visual symptoms combined with no reduction in size of pituitary mass, she underwent trans-sphenoidal surgery. Histology confirmed benign adenoma. She subsequently reported resolution of her headaches and improvement of her colour vision. Thyroid ultrasound (USS) identified a 5.4 mm × 2.7 mm U3 nodule in the right lobe and a 4.2 mm × 2.5 mm U2 nodule in the left lobe. Cytology following USS-guided fine needle aspiration of the right U3 nodule concluded papillary thyroid carcinoma (THY5). A formal referral was made to endocrine surgeon for the management of her papillary thyroid carcinoma. She made an uneventful recovery following thyroid and pituitary surgeries with acceptable thyroid function tests of TSH 0.26 mU/l, freeT4 19.6 pmol/l, freeT3 5.1 pmol/l, normal gonadotropins and prolactin 9 mU/l. She continued on levothyroxine 100 micrograms and hydrocortisone 25 mg in divided doses with cessation of cabergoline.
Conclusion
This case highlights the need for a full and thorough examination, which is the most basic but fundamental code of clinical practice and may well lead to the finding of other coexisting pathology in patients, despite singular presentation.

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EP289

Clinical and endocrinological evaluation of patients with empty sella

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Empty sella (ES) is characterized by herniation of the subarachnoid space within the sella, compression and flattening of the pituitary gland. Stretching of the pituitary stalk may also be seen. Empty sella is a frequent finding (5–23%) in autopsy series while it is < 0.01% in persons who undergo medical attention. Meanwhile there is an increase in sellar emptiness with age. Regarding pathophysiology and etiology, it may be primary to the incompetence of the diaphragma sellae and herniation of CSF in to the sella turcica. It may be secondary to pituitary autoimmune disease, brain trauma, radiation, surgery, hemorrhage, or infarction of the pituitary gland. Primary and secondary ES can be thought of and treated as one entity. As a master gland of endocrine system, hormone secretions from the pituitary gland should be evaluated if the patients have symptoms. The most common symptom associated to ES is headache. In patients with primary ES, radiological ES is found incidentally on brain MR mostly performed because of headache. Symptoms associated with endocrine abnormalities may be seen especially in those with secondary ES. We evaluated 30 patients with ES [23 female (24–80 year-old), 7 men (32–85 years-old)]. Basal hormone levels were measured and then stimulated hormone levels were evaluated if necessary by means of insulin tolerance test. In female patients: primary and secondary ES were seen in 19 and 4 patients respectively. In male patients primary and secondary ES were seen in 4 and 3 patients respectively. In women, secondary causes were 1 Sheehan syndrome, 1 transsphenoidal operation and 1 brain trauma and 1 related to Neuro-Behcet's disease. In men, secondary causes were 1 subarachnoid haemorrhage, and 1 transsphenoidal operation and 1 brain trauma. In women with primary ES, mild hyperprolactinemia (6/19), secondary hypothyroidism (5/19), GH deficiency (2/19), and panhypopituitarim (1/19) were found. One woman had primary hypothyroidism, 3 women had adrenal adenoma (1 Conn syndrome, 2 women had nonfunctional adrenal adenomas (1 unilateral, 1 bilateral) and 2 women had intracranial hypertension with primary ES. Type 2 DM and hypertension and obesity were frequent findings in women with primary ES. In men with primary ES, 2 men had panhypopituitarism, 1 patient had mild hyperprolactinemia, 1 had secondary hypothyroidism with GH deficiency. In men with secondary ES, 2 men had hypogonadotrophic hypogonadism and one man with subarachnoidal haemorrhage had normal pituitary function. Obesity and DM were not frequent in male patients with ES.

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EP290

Clinical and hormonal pecularities of acromegaly patiernts from ukrainian centre

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Introduction
Acromegaly (ACRO) is a rare disease of an excessive somatic growth and distorted proportions arising from hypersecretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). The aim Of this study is to investigate basic demographic parameters such as the age and gender related features, age at diagnosis of the disease, its clinical manifestations, biochemical control and structure of complications in Ukrainian patients with ACRO in a single neuroendocrinological centre.
Material and methods
Patients with ACRO: $n = 133$ [including 47 *de novo*]: female – 88, male – 45, and retrospective study 133 patients (female – 91, male – 42) who had neurosurgical treatment. Diagnosis of ACRO was based on the Consensus Statement on acromegaly (2018). The levels of PRL, GH and IGF-1 were measured.
Results
The study has established that 88.8% of the overall sample consist of patients aged 31 to 60 years: 26.5%/55.2% (male/female); $\chi^2 = 15.47$; $P = 0.0001$. Peak of the ACRO manifestation in the overall sample falls on the age of working efficiency (41.3 ± 12.0) yrs. Analysis of the complaints structure in patients with ACRO was: fatigability (45.5%), asthenia (43.9%), headache (43.9%), and excessive sweating (42.3%). Increasing sizes of hands and feet (60.2%) and in facial features (42.3%), which are specific morphological markers of ACRO, more than 50% of patients consider as age-related. It has been established that pre-nosological period has a linear proportional increase, related with age in patients with ACRO: ($R^2 = 3.4\%$; $P = 0.041$) and is also associated with the age of manifestation ($R = 0.24$; $R^2 = 5.96\%$; $P = 0.007$).

Conclusion
Sexual dimorphism of the clinical course ACRO is manifested at a young age at the time of manifestation of the disease and is characterized by a higher secretory activity of GH-secreting adenoma and it greater mass effect in men. Secretory and proliferative activity of the GH pituitary adenoma is associated with the age of the patient at the time of the manifestation of ACRO. High total secretory activity of GH-secreting pituitary adenoma, tumor growth rate, resistance to treatment and predisposition to relapse, which are associated with the young patient at the time of the manifestation of the disease, determine the 'fast-moving' flow of ACRO. In elderly patients, the domination of the secretory over the proliferative activity of the GH-pituitary adenoma and the satisfactory sensitivity to the treatment determine the 'slowly progressive' clinical course of disease.

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EP291

Cabergoline treatment: The ethics around side effects

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Cabergoline has long been used to treat prolactinomas for symptomatic, radiological and biochemical resolution of pituitary tumours. As clinicians we are well-versed at screening for physical side effects, but are we holistic enough? We present two cases illustrating the damaging social consequences of cabergoline treatment for prolactinomas.
Case 1
A 49-year-old married father of two presented with a seizure in April 2018. MRI showed 2.3 × 2.5 × 2.5 cm sellar and suprasellar mass which compressed the optic chiasm as well as an unrelated grade 2 oliogodendroglioma which was later debulked. Prolactin levels at presentation were 50.205. The remainder of his pituitary profile showed TSH 0.75, T4 9.5, ACTH 6.9, cortisol < 28, LH 0.9, FSH 1.3, testosterone 1.7, GH < 0.05. He was started onto cabergoline 500 mg twice weekly and 4 mg prednisolone daily. His prolactin fell from 50.205 to 816 over 5 months. Eighteen months later, he reported a change in sexual behaviour, the use of escort services and sexual involvement with work colleagues. Cabergoline was discontinued in November 2019. Repeat prolactin levels in December 2019 were 583 and testosterone of 12.
Case 2
A 56-year-old man in a long term steady same- sex relationship, presented with erectile dysfunction and low energy in October 2018. His prolactin was 3.464 and testosterone 4.5. The remainder of his pituitary profile revealed TSH 1.07, T4 11.3, cortisol 189, LH 1.8, FSH 2.1, testosterone 4.5 and SHBG 41. An MRI scan of his pituitary revealed a 11 × 9 mm pituitary adenoma. He was commenced onto Cabergoline 250 mg once weekly. His prolactin fell from 2464 to 18 within 5 months, with testosterone levels of 18.9. In October 2019, his worried partner reported a change in personality and hypersexuality. Cabergoline was stopped. However, due to the patient's concerns of a return of low libido, testosterone replacement was commenced. His prolactin in November 2019 was 1942. These cases raise important ethical questions. Firstly, how much of the hypersexual behaviour observed is a direct side effect of dopamine agonist treatment and how much is a behavioural consequence of the rise testosterone? Secondly, when cabergoline treatment results in behavioural side effects such as the failure of a marriage or financially crippling gambling, who takes responsibility when huge debts emerge and family units collapse? We must be cautious when prescribing and monitoring dopamine agonist therapy to avoid social harm to patients and balance this with depriving patients of effective non-invasive treatments.

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EP292

Quality of life in patients with Cushing's syndrome in remission: 10-year follow-up

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Introduction
Cushing's syndrome (CS) has been associated with low quality of life, even after biochemical cure. However little data is available on long term follow-up. The aim of the study was to analyse 10-year follow-up of quality of life (QoL) in patients in remission of CS.
Methods
24 patients in remission of CS followed in Hospital Sant Pau were included in this study (3 men, 21 pituitary origin, 3 adrenal; mean baseline age 45.1 ± 14.1). They performed their yearly clinical follow-up visits (including clinical and analytical parameters) and the same day completed 2 QoL questionnaires (EuroQoL and CushingQoL). This was performed both basally (at least one year after cure) and after 10 years (± 6 months).
Results
After 10 years, a decrease in QoL was found. Mean CushingQoL scores at first evaluation were 64, vs 58 after 10 years (P <0.001, scores worsened in 70.8% of the patients), while for EuroQoL-VAS basal scores were 73 vs 64 after 10 years (P = 0.002, scores worsened in 58.3% of the patients). Two patients had a recurrence at 10 year follow-up, but results did not change when both patients were excluded from the analysis (P < 0.001 for both questionnaires). The percentage of patients reporting problems in the 5 dimensions of EuroQoL at both evaluations was: mobility (28% vs 40%), self-care (12% vs 20%), usual activities (32% vs 32%), pain/discomfort (52% vs 64%), and anxiety/depression (44% vs 52%). CushingQoL and EuroQoL-VAS scores after 10 years correlated with baseline scores (CushingQoL P = 0.003, R = 0.586; EuroQoL-VAS P = 0.002, R = 0.605), but did not correlate with diagnostic delay, time since surgery, current urinary free cortisol, plasma cortisol, late-night salivary cortisol, ACTH, blood pressure, BMI or age.
Conclusion
QoL in patients in remission of CS worsens after 10 years, and correlates with baseline scores. Interventions to improve quality of life at early stages may help to prevent further deterioration in the future.

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EP293

Pasireotide LAR in acromegaly resistant to first generation somatostatin analogs – single-center prospective interventional study

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Introduction
The treatment of choice in persistent acromegaly after transsphenoidal adenomectomy is pharmacological treatment with first generation somatostatin analogs. They are effective in 25% to 45% of patients. Second generation somatostatin analog – pasireotide seems to be more effective.
Aim
The aim of the study was to assess the efficacy and safety of pasireotide LAR in acromegaly patients resistant to first generation somatostatin analogs.
Material and methods
Twenty eight patients (males n = 15, 53.6%, mean age 43.59 ± 13.48 years) with acromegaly after surgical debulking resistant to first generation somatostatin analogs were involved in the study. Four patients had radiotherapy performed 59, 23, 18 and 24 months before study beginning. Poor diabetes management was an exclusion criterion. All patients started with pasireotide LAR 40 mg every 28 days and had GH, IGF-1, glucose and HgbA1c measured every three months. Patients who did not achieved biochemical control of acromegaly after three-month treatment had the dose escalated to 60 mg if pasireotide tolerability and adverse events allowed. Dose reduction to 20 mg was performed in one patient with full biochemical control and difficulties with diabetes management. Within the study period 16 patients completed twelve-month treatment.
Results
After twelve-month treatment a significant decrease in GH (4.06 IQR: 1.86–6.37 μg/l vs 1.3 IQR: 0.9–2.92 μg/l, P = 0.0005) and IGF-1 concentration (605.63 ± 203.05 ng/ml vs 381.46 ± 201.82 ng/ml, P <0.0001, i.e. 2.39 ± 0.8 × ULN vs 1.51 ± 0.82 × ULN, P < 0.0001) was observed. The increase in fasting glucose concentration (106, 95 ± 13.85 mg/

dl vs 120.46±17.76 mg/dl) and glycated hemoglobin (5.91±0.44% vs 6.39±0.63%) were also significant ($P=0.002$ and $P<0.0001$ respectively). In five patients 5/16=31.3% GH concentration fell below 1 µg/l and in twelve GH concentration was below 2.5 µg/l (12/16=75%). In five patients (5/16=31.3%) IGF-1 concentration was within normal limits after twelve-month treatment and in ten patients IGF-1 concentration was below 1.5 × UNL (10/16=62.5%). Three patients (3/16=18.8%) achieved full biochemical normalization after one-year treatment with pasireotide LAR.
Conclusions
Pasireotide LAR is more effective than first generation somatostatin analogs in patients with persistent acromegaly after surgical debulking. Carbohydrate metabolism should be regularly monitored on pasireotide treatment.

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EP294

Challenges in management and pharmacotherapeutic strategy in patients with a prolactinoma and neuropsychosis; a case presentation and literature review

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A 36-year-old male presented to the emergency department with a 24-hour history of mutism, paranoia and 3-day history of social withdrawal. He was unable to engage with healthcare professionals and the history was elicited from his mother. Due to a background of mild depression, an acute psychotic diagnosis was initially pursued. A CT scan on admission revealed a large pituitary lesion. A pituitary MRI scan thereafter demonstrated a large 25 × 30 × 18 mm sellar and suprasellar pituitary macroadenoma involving the left cavernous sinus and internal carotid artery, protruding into the left cranial fossa and displacing the optic chiasm. Biochemical investigations revealed a serum prolactin level c.66.000 mIU/l with biochemical hypogonadism (testosterone 3.3 nmol/l, LH 1.7 IU/l). Clinical examination revealed no ophthalmoplegia nor visual field deficits. He was unable to engage with formal visual-field testing initially, however these later demonstrated a superior bilateral deficit. Capacity assessment on admission demonstrated a lack of mental capacity so a best interests decision for medical management was made jointly by Psychiatry and Endocrinology teams. He was commenced on the antidepressant sertraline and the antipsychotic aripiprazole (10 mg daily), a partial dopamine agonist. Aripiprazole was chosen to treat both hyperprolactinaemia and psychotic symptoms, whilst avoiding potential neuropsychiatric side effects of ergot-derived dopamine agonists. After two weeks of therapy, his prolactin fell to c.38.000 mIU/l and his mental status had improved. However, by two months, he reported weight gain, fatigue, leg cramping and stiffness, whilst blood tests showed a prolactin rise to c.55.000 mIU/l. At this point aripiprazole was not felt to be of any further benefit and was switched to cabergoline, initially 250 mg once weekly and quickly up-titrated to 500 mg twice weekly. By month six, his prolactin had fallen to c.3.500 mIU/l and his testosterone (9.8 nmol/l) and LH (0.8 IU/l) showed improvements. Repeat MR imaging demonstrated a reduction in macroadenoma size with decompression of the optic chiasm. Currently at month eight, his mood has normalised. His prolactin however has risen to c.4.500 mIU/l so cabergoline has been increased to 750 mg twice weekly. This case highlights the challenges presented by the combination of neuropsychiatric symptoms and a functioning macroprolactinoma. Initial medical management with aripiprazole monotherapy can be used to treat psychiatric disease without worsening prolactin levels. We have identified seven case reports published since 2007 of aripiprazole being used for patients with prolactinomas who have coexistent psychiatric symptoms [1–7]. These cases describe the use of dopamine agonists concomitantly or first, with aripiprazole to minimise the side effects.

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EP295

Pre-operative full blood count, C-reactive protein and serum inflammation-based scores may predict aggressive or refractory disease in patients with pituitary adenomas

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Introduction
Full blood count (FBC), C-reactive protein (CRP), albumin and serum inflammation-based scores reflect systemic inflammation and predict outcomes in oncological patients. While these are increasingly used in cancer, little is known in pituitary adenomas (PAs). We aimed to characterise FBC and inflammation-based scores in patients with PAs and investigate the usefulness of such parameters in predicting aggressive/refractory disease.
Methods
We studied 424 PA patients (68 prolactinomas, 72 acromegaly, 70 Cushing´s disease, 208 non-functioning PAs (NFPAs) and 6 thyrotrophinomas), as well as 47 craniopharyngiomas (CP) and Rathke's cleft cysts (RCC). Patients who had first operation at our centre between 2006–2019 and available pre-operative biochemical data (FBC, CRP, albumin) were included. Patients with infection, malignancies, autoimmune or haematological conditions, and those on supraphysiological glucocorticoid doses at the time of blood test were excluded. The following scores were considered: Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Lymphocyte-to-Monocyte Ratio, Systemic Inflammation Index (SII), Neutrophil-Platelet Score (NPS), Prognostic Nutrition Index (PNI), and Glasgow Prognostic Score (GPS).
Results
PA patients had lower CRP, GPS, and higher PNI than CP/RCC patients. Cushing´s disease patients had higher mean platelet count, leucocytes, neutrophils and monocytes, and higher NLR, NPS and SII than other subtypes. FBC and inflammation based-scores didn't differ among other non-Cushing's subtypes. Serum prolactin correlated negatively with NLR among prolactinoma patients, while in acromegaly IGF-1 levels correlated positively with platelet count. Within Cushing´s disease, serum cortisol and ACTH correlated respectively with leucocyte count (positively); 24 h-urine cortisol levels correlated negatively with platelet, eosinophil and basophil counts, and were higher in patients with elevated CRP and GPS. Patients with functioning non-Cushing PAs and with suprasellar extension, cavernous sinus invasion, hypopituitarism and those requiring reoperation had higher GPS, while raised NPS was associated with suprasellar extension and active disease at last follow-up. Cushing´s patients with more invasive and refractory tumours had fewer platelets at diagnosis. NFPA patients who suffered apoplexy had more leucocytes, neutrophils and monocytes and higher CRP. NFPA patients suffering recurrence and requiring reoperation had fewer lymphocytes and higher PLR.
Conclusions
CP/RCC patients have higher systemic inflammation than PA patients. FBC and inflammation-based scores remarkably differ in Cushing´s disease comparing to other PA subtypes. The extent of pituitary hormone excess may influence, at least in part, the systemic inflammation in functioning PAs. Some inflammation-based scores may predict aggressive/refractory PA disease, namely GPS in functioning PAs (including Cushing´s disease), NPS in functioning non-Cushing PAs and PLR in NFPAs.

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EP296

Prevalence of hypocortisolism and replacement treatment after transsphenoidal surgery pituitary adenomas

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Aim
Evaluation of hypocortisolism and replacement treatment after transsphenoidal surgery pituitary adenomas and subsequent follow-up in Endocrinology offices.
Material and method
We conducted a retrospective intra-subject study of patients with pituitary adenomas who were undergone surgery. Clinical and analytical data were evaluated at baseline and after surgery between 2012–2018.

Results
30 patients (50% women) were analyzed. Mean age 48.6±12.1 years, mean size of adenomas 2±1.1 cm (26.7% microadenomas and 73.3% macroadenomas) and mean time after surgery 1.4±0.5 months. Before surgery, we observed 16.7% hypothyroidism, 3.3% somatotrophic hormone deficiency, no cases of hypocortisolism or hypogonadism and 33% of subjects had campimetric alterations. After surgery, we detected 34.8% hypothyroidism, 27.6% somatotrophic hormone deficiency, 40% hypogonadism and 10% insipidus diabetes (in 6.7% of cases it persisted after a year). Campymetry improved by 66% (50% complete resolution, 22% unchanged and 11% worse). Regarding post-surgery basal cortisol, 23.3%<3 mg/dl, 33.3% 3–11 mg/dl, 26.7% 11–18 mg/dl and 16.7%>18 mg/dl. Ten percent required reevaluation (66% 1 mg ACTH test and 33% insulin hypoglycemia). Mean dose of corticosteroid replacement therapy was 25.7±9.6 mg/day at hospital discharge, 16.5±12/day mg at first visit after surgery and 12.6±14.4 mg/day after a year.
Conclusions
We observed a significant incidence of hypogonadism after surgery. Campimetric affectation improved in most of patients. Hypocortisolism was present in 56.6% of subjects after surgery and they needed corticosteroid replacement therapy. Less than 50% of patients were treated unnecessarily. New strategies to select patients who need replacement steroid treatment are needed.

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EP297

Treatment outcomes of acromegaly: A single-centre experience

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Introduction
The purpose of this study was to evaluate treatment options and effectiveness in patients with acromegaly.
Methods
The study involved retrospective data collection from charts of 75 patients with acromegaly who was treated at Vilnius University Hospital Santaros klinikos.
Results
Patient population consisted of 21 males (28%) and 54 females (72%), mean age at diagnosis 52±13 years. In most of the cases, macroadenoma was diagnosed (macroadenoma 68.75% vs microadenoma 31.25%). Based on GH and IGF-1 levels, disease control was achieved in 33 out of 73 (45.2%) patients (data of 2 patients is missing). Transsphenoidal surgery was performed in 49 (67.1%) patients of which disease control was achieved in 27 (57.4%): in 13 out of 19 patients without additional treatment, in 8 out of 22 with additional medical therapy and in 6 out of 7 with additional medical therapy and radiotherapy. Permanent postoperative hypopituitarism was observed in 9 (18.4%) patients. Disease control was achieved in 6 out of 24 (25%) patients who refused or had contraindications to surgical treatment. Medical therapy (somatostatin analogues (SSA), dopamine agonists (DA)) was applied in 38 of our patients: 27 patients received first-generation SSA, 3 patients received Pasireotide, 3 patients DA and 5 patients SSA with DA (control was achieved in 8 (29.6%), 1 (33.3%), 2 (66.7%) and 1 (20.0%) respectively). High-dose medical therapy are now receiving 18 out of 38 patients and in a majority (94.4%) of them complete disease control was not achieved.
Conclusions
Surgical treatment is the first-line treatment option of acromegaly, although many patients refuse or have contraindications for the surgery. Primary medical therapy with SSA±DA leads to disease control in only 25% of the patients despite availability of high-dose first generation SSAs and pasireotide. The best outcomes of acromegaly treatment were observed when treatment combinations were chosen – surgery with secondary medical treatment±radiotherapy.

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EP298

Dabigatran-induced pituitary apoplexy in young patient: A case report

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Introduction
Pituitary apoplexy is defined as the acute onset of clinical symptoms associated with hemorrhage or infarction within a normal pituitary gland or previously known pituitary adenoma.
Case report
A 47-year-old hypertensive Caucasian male patient with a known pituitary macroadenoma and family history of pituitary adenomas, was treated with thromboprophylaxis after a meniscus surgery. He was on treatment with non-steroidal anti-inflammatory medication for knee pain relief, and sartan for mild hypertension. He had been taking low molecular weight heparin for one month, but had changed the anticoagulant to dabigatran etexilate 150 mg/day, after the occurrence of deep thrombophlebitis. Over the next 3 days, the patient complained of increasing bilateral frontal headaches with the onset of binocular diplopia, drowsiness, head paresthesia and nausea. On admission, the patient was alert and had bilateral temporal hemianopia. Brain magnetic resonance imaging (MRI) showed a 1.6 cm pituitary mass with hemorrhage (apoplexy) and extension to the left cavernous sinus, with right deviation of the pituitary stalk and optic chiasm compression. Transsphenoidal resection of the tumor was done which resulted in tumor ablation and symptoms amendment.
Endocrine testing
Two weeks after transsphenoidal surgery showed thyrotroph and gonadotroph hypopituitarism. The pathology report confirmed a nonfunctional pituitary adenoma with intratumoral hemorrhage and immunohistochemistry positive for SYN and panCK, p53<1%, Ki-67<1%.
Conclusion
This case illustrates the risks of anticoagulation in patients who are already known to have a pituitary adenoma, this condition should be considered as a relative risk for anticoagulation, even with modern drugs as dabigatran.

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EP299

Non-functioning pituitary adenomas – clinical presentation and management, experience of a tertiary centre in Romania

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Background and aim
Non-functioning pituitary adenomas (NFPAs) are hormonally inactive adenohypophyseal tumors. The absence of hormone hypersecretion and the lack of clinical manifestations delay the diagnosis and therefore symptoms of mass effect are frequently seen in NFPAs. The primary endpoint of this study was to evaluate the clinical presentation of patients with NFPAs and their therapeutic management. The secondary endpoint was to identify how gender and tumor size impact the clinical presentation and therapeutic management.
Patients and methods
We evaluated 98 patients diagnosed with clinically and biochemically NFPAs between January 2013 and January 2018. Anamnestic data, symptoms at presentation, pituitary function and imaging, treatment option and outcomes were analysed.
Results
68 of the patients were female (69.39%) and 30 male (30.61%), with a mean age of 43.61±18.42 years. The most common symptom at presentation was headache (30.61%), followed by diplopia (13.27%) and bitemporal hemianopsia (13.27%), ptosis (9.18%), quadranopsia (1.02%). The prevalence of endocrine disorders caused by pituitary stalk compression was 22.9% for hyperprolactinemia and 6.9% for diabetes insipidus. GH deficiency was the most prevalent pituitary hormone deficiency (41.3%), followed by TSH deficiency (22.81%) and gonadotropin deficiency (15.31%). More than half of NFPAs were diagnosed as microadenomas (50.67%). The most used approach was conservative management (69.39%), followed by surgery (22.45%), radiation therapy (4.08%), surgery and radiation therapy (4.08%). Tumoral recurrence was seen in 6% of patients who underwent surgery, radiation therapy or both. The age at diagnosis was significantly higher in

men, compared to women (49.41±20.8 vs 41.1±16.85 years, $P=0.042$). Moreover, macroadenomas were more common in males than in females (85.71% vs 35.19%, $P<0.001$). When dividing the patients based on tumor size we found a higher age at diagnosis for macroadenomas, compared to microadenomas (51.97±17.07 vs 34.38±15.19 years, $P<0.001$), but also different treatment strategies: in microadenomas conservative management was chosen in 97.37% and surgery in 2.63% of patients, while in macroadenomas surgery was preffered in 40.54% and conservative management in 45.95% of patients ($P<0.001$).

Conclusions

NFPAs are characterized by heterogeneity in clinical presentation, patients usually presenting with symptoms of mass effect or hipopituitarism. In this regard our data showed a high prevalence of GH deficiency, while headache was the most common mass effect symptom. Although there was an overall female predominance for NFPAs, most macroadenomas were diagnosed in men. Furthermore, tumor size dictates the therapeutic management, with surgery being indicated mostly in macroadenomas.

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EP300

Development of a digital patient-provider communication tool to facilitate shared decision making for patients with non-functioning pituitary adenomas: InvolveMe

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Background

Patients report a variety of persisting symptoms that reduce their quality of life after treatment for non-functioning pituitary adenomas (NFPA). Digital tools have the potential to improve patient-provider communication and patient outcomes by giving opportunities for patients to report their current status, which can be helpful in recognizing symptoms and identifying needs. Mapping patients' symptoms, needs and preferences prior to the consultation can aid in preparation, set the agenda for the consultation and facilitate involvement in the decision-making processes.

Aim

The aim was to map symptoms, needs and preferences for software features that should be included in the development of a digital communication tool, *InvolveMe*, to support shared decision making in the follow-up of patients with NFPA.

Method

A combination of interviews with patients and a focus group with health care providers (HCP) was conducted. Participants were recruited from an outpatient clinic at a tertiary referral center with long lasting experience in treating pituitary patients. Data were analyzed using thematic analyses, which informed the content and software development. The development process was supported by more tool development workshops.

Results

Analyses from interviews with patients ($n=5$) and a focus group with HCPs ($n=5$) generated tree main themes: 1) Making symptoms and challenges visible, 2) Mastering a new life, and 3) Digital opportunities for follow-up. Theme 1 and 2 gave input for content development of the symptom and needs assessment part of the tool. The patients expressed need for a variety of bodily symptoms and psychosocial challenges to be addressed, including pain, fatigue, anxiety and loneliness. The patients described the need for work related support and information related to living a healthy life with the newly established condition. Theme 3 provided input for software development of the InvolveMe tool, including integration with an existing patient portal already in use by patients and providers. The HCPs perspective was in line with and elaborated on the patient perspective. Tool development workshops with patients ($n=3$) and HCPs ($n=3$) supplemented the development process and ensured that important topics were discussed and further elaborated.

Conclusion

Inclusion of content and software features relevant and meaningful for patients as well as HCPs was ensured by stakeholder involvement, from study initiation through exploration, design and development. To explore usability and potential effects of the *InvolveMe* tool, a feasibility pilot is currently in progress testing content and software features in clinical practice and context.

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EP301

Can you predict the success of surgery in cushing's disease?

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Objective

Cushing's disease (CD) is difficult to diagnose because of its rarity and because its most common symptoms can overlap with those of other more common conditions. Remission rates in the postoperative vary between 55–85%. Overall, the mean time to diagnosis was 38 months. The objective of this study was to describe whether there is any pre-surgical clinical data that predicts CD remission after TSS.

Patients and methods

Retrospective analysis of patients who underwent as TSS for CD. Variables analyzed: age, sex, time to diagnosis, tumor size, serum cortisol, salivary cortisol, urinary-free cortisol (UFC), remission of CD. Remission was defined as normalization of serum cortisol, salivary cortisol and UFC levels.

Results

67 patients with CD treated with TSS. 42.45±14 years old. Women: 82.1%. Macroadenomas 49.3%. Remission 71.6% (men: 3; women 45). Persistence 28.4% (men: 9; women 10). Presurgical treatment (76.2%): 44 patients with ketoconazole, 1 patient with cabergoline and 6 patients with combination of both (remission: 84.8%, persistence: 57.9%; $P=0.04$). Recurrence: 23.9%. Death 4.5% ($n=3$).

	Remission	Persistence	*P*
Age (years)	41.17±14.82	45.68±13.24	0.7
Time from onset of symptoms to diagnosis (months)	34.52±28.96	23.33±29.75	0.2
Time from diagnosis to surgery (months)	6.5±5.6	5.7±3.37	0.5
Tumor size (mm)	9.35±6.87	20.47±9.55	0.001
Basal cortisol (µg/dl)	23.6±10.64	22.10±9.37	0.6
Midnight plasma cortisol (µ g/dl)	14.52±5.38	34.6±32.47	0.015
Midnight salivary cortisol (µg/dl)	2.75±6.71	0.74±0.56	0.04
24-hour urinary cortisol (µg/24 h)	586.23±678.55	277.42±190.41	0.05
ACTH (p g/ml)	81.14±50.5	81.8±72.12	0.96

Conclusions

Remission is more frequent in women and in patients with pre-surgical treatment. In the presurgical study, patients in remission had smaller tumors and lower cortisol levels at midnight, however they had higher levels of CLU.

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EP302

Long-term outcomes of prolactinoma-related pregnancies

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Objective
The aim of the study is to evaluate both the long-term consequences of exposure to dopamine agonists (CAB and BRC) at the beginning and during pregnancy, and the effects of pregnancy on remission.
Methods
Thirty-seven prolactinoma patients who developed 58 pregnancies while receiving DAs treatment were included in this retrospective study. Age of gestation; both maximum residual tumor diameter and PRL levels before conception; the course of prolactinoma during and after pregnancy; the outcomes of pregnancies; comorbidities and complications during pregnancy and health of fetus were evaluated. Remission was defined as regained normal gonadal function with normal PRL level after discontinuation of DA therapy.
Results
58 pregnancies occurred under BRC (n:40) and CAB (n:18). The mean gestational age was 30±5 years (range 20–39), the mean maximum tumor diameter before pregnancy was 6.3±3.5 mm, and median PRL level was 32 ng/dl (range 1–15). Average treatment period until conception is 9 months for BRC and 7 months for CAB. Average cumulative CAB dose was 5mg for the first 6 weeks of gestation. BRC and CAB was discontinued in patients whose adenoma decreased significantly before conception, while the others continued throughout the pregnancy (n:13). No one had visual complaints during their pregnancy. Eighty-one percent of pregnancies resulted with live birth (15 CAB/33 BRC) and 19% with spontaneous abortion (3 CAB/8 BRC). The mean follow-up time after gestation was 7.5±5.5 years (range 1–23). Among the babies, one Down syndrome (mother's exposure was 325mg BRC during gestation) and one low birth weight baby (mother's exposure was 2 mg CAB during first weeks of gestation) were seen. Gestational diabetes was detected in 3 mothers (2 CAB/1 BRC). In the pituitary MRI after cessation of lactation, the tumor disappeared in 8 and was stable in others. Data on postpartum menstrual periods were available in 44 cases, and cycles were spontaneous in 31% of them. After delivery, 32% of the patients (4 CAB/8 BRC) were found to be in remission for 6.5 years. Other than one, all children are healthy and successful in a period of up to 23 years.
Conclusion
No side effects of DA exposure on fetus development were observed at the beginning of pregnancy or during pregnancy. Because of the possibility of spontaneous menses patients should be carefully evaluated before re-administration of DA.

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EP303

Metastasis of lung cancer to two different endocrine organs

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Both pituitary and adrenal gland metastases of lung cancer are very rare. A 79-year-old male patient with diabetes mellitus and hypertension was admitted to our hospital because of a mass in the lungs of the thorax CT. TSH: <0.005 UIU/ml (0.27–4.2), free T4: 0.794 ng/dl (0.93–1.7). Other pituitary hormones were also examined: FSH: 0.708 mIU/ml (1.5–12.4), LH: <0.1 mIU/ml (1.7–8.6), prolactin: 12.7 ng/ml (4.04–15.2), total testosterone: <0.025 ng/ml (1.93–7.4), cortisol: 1 µg/dl (6.02–18.4) was found to be. Pituitary MRI showed an infiltrative mass in the hypothalamus and stalk. PET/CT showed a malignant mass in the right hilar area, metastatic lymph nodes in the mediastinum, and diffuse metastasis in the left adrenal and bones. Pathological diagnosis in trucut needle biopsy from the right supraclavicular lymph node: Reported as metastasis of non-small cell lung carcinoma. The pituitary and adrenal masses were accepted as lung cancer metastasis. The patient was started on prednisolone 5mg, levothyroxine 25 µg/day. Diabetes insipitus was not considered due to lack of increase in urine volume and normal urine density and serum sodium levels. Patient oncology and radiation oncology were consulted and radiotherapy and chemotherapy were planned. Although fatigue is a common symptom in lung cancer cases, it should be kept in mind that metastasis to the pituitary and/or adrenal gland may occur in these patients

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EP304

Bilateral inferior petrosal sinus sampling in a cohort of patients with acth dependent cushing´s syndrome in a tertiary hospital

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Objectives
To describe the results of the bilateral inferior petrosal sinus sampling (BIPSS) performed in our hospital for differential diagnosis between Cushing disease (CD) and ectopic ACTH secretion (EAS), and evaluate if CRH stimulation during this test improves its diagnostic accuracy.
Material and methods
We retrospectively review 29 BIPSS performed in 26 patients (4 men, 22 women), with mean age of 44.7 year-old (range 28–69), diagnosed with ACTH-dependent Cushing´s syndrome and followed in the Endocrinology and Nutrition Department of La Paz University Hospital from 2001 to 2019. All BIPSS were performed using CRH stimulation; ACTH and prolactin levels were determined at baseline and three, six and ten minutes post-stimulation. A central-to-peripheral ACTH gradient ≥2.0 at baseline or ≥3.0 after CRH stimulation was the cut-off to diagnose CD and central-to-peripheral prolactin ratio ≥1.8 was considered successful catheterization of the inferior petrosal sinus (IPS). The gold standard to confirm CD was the histological finding of ACTH-secreting pituitary adenoma and/or remission after surgery.
Results
In 17 (58.6%) of the 29 BIPSS performed, both IPS were successfully catheterized, in 8 (27.6%) only the right was catheterized, in 3 (10.3%) it was only the left and in 1 (3.4%) no IPS was catheterized. Of the 28 BIPSS with at least one IPS correctly catheterized, 24 (85.7%) diagnosed CD; 21 of these patients went to surgery and only 8 (38.1%) had histology of ACTH-secreting pituitary adenoma, 10 patients had no pathological findings and the histopathology reports of the other patients were not found. All patients with histological findings of adenoma and other 5 patients without findings got into remission; therefore in 13 patients (61.9% of operated patients) CD was confirmed. The other patients underwent computed tomography and Octreoscan that did not show any tumor suggestive of EAS, so their diagnosis remains indeterminate. Three patients with positive BIPPS result are currently waiting for surgery. Among the 4 BIPSS that ruled out a pituitary ACTH hypersecretion, EAS was confirmed in 2 patients (3 BIPSS). All patients with a positive BIPSS result and diagnosis of CD confirmed by histology and/or remission, had baseline central-to-peripheral ACTH gradient >2.0 (sensitivity 100% at baseline), and >3.0 after CRH (sensitivity 100% post-stimulation).
Conclusion
BIPSS allowed a right diagnosis in the 100% of our patients with CD or EAS subsequently confirmed by histology and/or remission, being a very highly sensitivity test. CRH stimulation did not improve the sensitivity of BIPSS in our patients.

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EP305

A case series of hypopituitarism presenting as nocturnal hypoglycemia in patients with type 2 diabetes mellitus

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We describe four female patients with T2DM, presenting with nocturnal dizziness (ND), low capillary blood glucose & low BP, that was partially relieved with oral glucose & salt water. C1: MB 66 years, on background of hypertension (HT, valsartan+hydrochlorthiazide (HCT)+amlodipine (AM)), hypothyroidism (T4D) (levothyroxine 700 mg/week) & IHD

(pEF) presented, 3 years into her diagnosis, A1c 52 mmol/mol, with unsteady gait, frequent falls (normal-neurology), swollen feet & generalised non-exertional fatigue. Four years into follow-up, A1c-41 & weight reduced by 3.8 kg. An evaluation was undertaken because of ND while on canagliflozin C/vildagliptin V/Met. C2: SB 64 yrs, (Met/gliclazide/Insulin treated), background of HT (nifedipine + metoprolol) & anxiety (antidepressants-AD) presented, 32 years into her diagnosis, A1c-52, with leg pains, unsteady gait (severe neuropathy) & unprovoked weight gain. After 5 year follow-up, stiffness & fatigue worsened. She lost 5 kg & A1c was 41 & evaluated for recurrent ND (RND) C3: SA 45 yrs old, C + V + Met treated, on background of HT (telmisartan + HCT), anxiety (AD) and T4D (T4 875 mg/wk) presented to us 4 years into her diagnosis, A1c-55, with complaints of generalised non-exertional fatigue and bodyache. After 1 yr of follow-up she gained 1.8 kg, A1c was 57 & evaluated for ND C4: MN 54 yr old, Met + sitagliptin + gliclazide treated, on background of anxiety (AD) & T4D (175 mg/day) presented, 6 years into her diagnosis, A1c-50, with complaints of extreme fatigue & pain in both legs (normal neurology). After 4 months she had RND despite stopping gliclazide Baseline tests suggested isolated GH deficiency (IGHD) in C1, 2, 3, C4 had panhypopituitarism, confirmed by glucagon stimulation test. MRI (pituitary) for C1, 2 & 3 was normal. C4 had non-functioning pituitary macroadenoma (removed transphenoidally). Three patients were initiated rGHT, titrated to mid-centile IGF-1 & followed for 1 year. C4 received hydrocortisone. BMI (C1:30.86–31.25; C3:39.72–40.09; C4:22.89–25.39), A1c mmol/mol (C1:43–48; C3:55–64; C4:48–82), urine microalbumin mg /mmol (C1:0.29–1.12; C3:1.36–2.45; C4:0.62–1.67) & HDL mmol/l (C1:0.93–0.98; C3:1.00–1.03, C4:1.12–1.293) increased. Hs-CRP nmol/L (C1:24.47–16.19; C3:90.57–75.14; C4:6.75–5.71), NT-ProBNP pmol/l (C1:10.40–3.33; C3:7.09–1.77; C4:8.39–2.36) & triacyglycerol mmol/l (C1:1.76–1.19; C3:1.58–1.21; C4:0.89–0.89) reduced. Hypopituitarism (IGHD) should be considered in T2DM patients presenting with nocturnal hypoglycaemia.

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EP306

Clinical description and management in a series of macroprolactinomas

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Introduction
The purpose of this study was to describe the clinical characteristics of patients with macroprolactinoma in a second level Hospital.
Methods
Retrospective data collection of patients diagnosed with macroprolactinoma between 2002 and 2017 at Jerez University Hospital.
Results
Complete Data were obtained from 22 patients. The mean age at diagnosis was 40.32 ± 18.3 years (men: 52.9 ± 14.2, women: 27.7 ± 12.4). 50% men (m) and 50% women (w). Prolactin levels at diagnosis: 856.8 ± 1139 ng/ml (m: 1253.6 ± 1332.3, w: 460 ± 779) and adenoma size at diagnosis: 20.6 ± 12.3 mm (m: 28.8 ± 12.6, w: 12.4 ± 3.2). The most common presenting symptom was hypogonadism/oligomenorrhea: 90.9% (m: 45%, w: 55), followed by headache 40.9% (m: 55.5%, w: 44.4%), galactorrhea 22.7% (w: 100%) and 9.1% with visual impairment at diagnosis. There were significant differences in tumor size at diagnosis ($P = 0.0001$), in tumor size after treatment ($P = 0.050$) and in the presence of galactorrhea ($P = 0.011$) between both sexes. Serum prolactin fell to a nadir of 31.5 ± 53.9 ng/ml and fell within normal limits in 71.4% of cases at 8.2 ± 3.9 months. An average dose of cabergoline of 1.5 ± 1.4 mg/week and bromocriptine of 5 ± 3.5 mg/d was used. Tumor size decrease was observed in 94.7% of patients, with a decrease in largest tumor diameter greater than 5.4 ± 4.7 mm (31.6 ± 34.7 months). One patient required surgery for being resistant to medical treatment. Visual disturbances at diagnosis improved after starting medical treatment. No cases of spinal fluid fistula or pituitary apoplexy were observed.
Conclusions
The response to medical treatment was adequate in the vast majority of patients with macroprolactinoma, without further complications. Diagnosis was made at an earlier age in women and tumor size at diagnosis was smaller in women than in men.

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EP307

Curability rate of cushing's disease 1 year posttreatment

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Background
Cushing's disease is characterized by chronic ACTH hypersecretion, leading to hyperplasia of the adrenal zonae reticularis and fasciculata and, therefore, increased secretion of cortisol, androgens and DOC. Cushing's disease is the most common form of Cushing's syndrome, being responsible for approximately 80% of reported cases.
Aim
To evaluate the curability rate of Cushing's disease 1 year postoperatively.
Subjects and methods
We studied retrospectively 28 patients from our Endocrinology department, between 2016–2017, with Cushing's disease: 14 patients that were treated by transsphenoidal adenomectomy and 14 patients by bilateral adrenalectomy, with and without radiation therapy and medical treatment.
Results
77% of the subjects were women and 23% were men. Age of the patients was between: 30–40 years (13%), 41–50 years (40%), 51–60 years (16%), 61–70 years (23%), 71–80 years (8%). 29/30 patients presented clinical features suggestive of cortisol hypersecretion: red to purple striae (53%), facio-cervico-truncal obesity (83%), hirsutism (40%), hypertension (73%) and diabetes (26%). Patients treated by transphenoidal adenomectomy had the following outcome: 57% had microadenomas that were cured postoperatively, 43% remaining had macroadenomas, of which: 66% were resistant to combined treatment- surgery, gammaknife radiation therapy and medical treatment with steroidogenesis inhibitors, somatostatine analogs or dopamine agonists and 34% were cured postsurgery. Patients with bilateral adrenalectomy: 79% cured postoperatively, of which 35.7% also underwent radiation therapy and 21% controlled after bilateral subtotal adrenalectomy combined with radiation therapy and medical treatment.
Conclusions
The elective treatment for Cushing's disease is removal of the pituitary adenoma, by transsphenoidal adenomectomy, which has a high rate of curability, predominantly when dealing with microadenomas. Bilateral adrenalectomy is a secondary treatment option, that cures Cushing's disease, but at the cost of adrenal insufficiency.

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EP308

Insipidus diabetes and vaginal ulcers... evidence for the diagnosis of langerhans cell hypophysitis

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Introduction
Langerhans Cell Histiocytosis (HCL) is a rare granulomatous disease, unknown etiology, with a wide clinical spectrum. The pituitary is affected in 25% of cases, with diabetes insipidus being the earliest and most frequent feature. Although it is more common in pediatric age, it can also be developed by adults.
Clinical case
A 39-year-old, caucasian, woman presents with polydipsia with 5L/day of water and an appetite for cold drinks, polyuria with nicturia and amenorrhea, with two years of evolution. In association, complaints of vaginal itching and dryness. She had been medicated with fluvoxamine, bisoprolol, zolpidem and alprazolam since an year ago for an anxiety disorder. On physical examination she presents with no characteristic biotipe, hemodynamically stable BMI 29.3 kg/m2. The gynecological examination revealed vesicular and ulcerated lesions of various dimensions and in different stages of healing in the vulvar region.
Analytically
A sodium of 152 mmol /l (135–145), a low urinary density (1003) and a low urinary osmolarity (108 mOsm/kg). All the other pituitary hormonal lineages were normal. A pituitary MRI revealed the absence of the hypersignal in T1 in the neurohypophysis and thickening of the pituitary stalk. Central diabetes insipidus was confirmed and she started on 0.06mg oral desmopressin 2 times/day, with improvement of symptoms. Given the persistence of

absence of menstruation, but without primary hypogonadism, we performed the LHRH stimulation test that was normal. The complementary investigation excluded autoimmune, infectious and neoplasic disease. The biopsy of a vulvar lesion and subsequent immunohistochemical revealed positivity for the CD1a and S100 markers, confirming HCL etiology. The involvement of organs such as the spleen, liver, lung and bone marrow were excluded. She started on chemotherapy with cladribine and a genital typical application of activated antifungal. The genital lesions disappeared although she remained in amenorrhea and with central diabetes insipidus in the pituitary MRI there has been no progression of the disease.
Discussion
This case intends to highlight a great heterogeneity of clinical manifestations caused by HCL, usually the definitive diagnosis is difficult to achieve. In this particular case the biopsy of the vulvar lesions gave the final diagnosis. It is not consensual that chemotherapy is beneficial for these patients although in this case seemed to help the healing of the vulvar lesions without progression of pituitary disease.

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EP309

Functional gonadotroph adenoma

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Introduction
The pituitary adenoma is the most frequent begnin pituitary tumor. They are labeled based on their size, tumors smaller than 1 cm called microadenomas and tumors bigger than 1 cm called macroadenomas. Moreover, they can be functional or non functional. Among the functional ones, gonadotroph adenomas represent 15 to 20%.
Observation
We report the case of a 27 years old women, who consulted for secondary amenorrhea for 1 year. Further hormonal examinations showed an elevated FSH level at 170 mUI/l and an elevated LH level at 81 mUI/l with no other abnormalities in the rest of the pituitary hormones.The MRI revealed a macroadenoma 11.5 × 12.4 mm in diameter strongly enhanced with gadolinium-based contrast agents.After a few years of surveillance, the patient developed a visual field deficit and a decrease in the visual acuity. She underwent lesional resection by the endonasal transsphenoidal approach complicated with panhypopituitarism.The analysis of the tumor samples revealed an immunopositivity for both FSH and LH.
Conclusion
In women, functional gonadotroph adenomas may cause ovarian stimulation syndrome and/or menstrual abnormalities. They are mostly macroadenomas and are associated with significant morbidity.The primary therapy remains surgical which can lead sometimes to full recovery.

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EP310

Familial X-linked kallman syndrome associated with ptosis, case series

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Kallmann syndrome is a rare congenital hypogonadotropic hypogonadism with variable degrees of hyposomia to anosmia. This syndrome can be transmitted as autosomal dominant, autosomal recessive and X-linked inheritance pattern. We are reporting two cases of young male siblings (17 and 16 years old) who are the offspring of unrelated parents, presenting with delayed puberty and both were complaining of hyposmia. Their older brother, aged 24 years, was diagnosed with isolated hypogonadotrophic hypogonadism. Both patients had eunchoid habitus with small penis and testis with Tanner stage 1. They had a history of cryptorchidism which was corrected with orchidopexy at an early age. The older sibling had unilateral congeital ptosis. Upon further testing, they were found to have hypogonadotropic hypogonadism with severely low Testosterone and undetectable Luteinizing hormone and Follicle stimulating hormone. Other pituitary axes were intact. Pituitary MRI showed normal pituitary with normal olfactory nerves. Chromosomal analysis of both siblings showed 46 XY karyotype with hemizygous likely pathogenic variant was identified in Kal 1 (ANOS1) gene, consistent with a genetic diagnosis of X linked hypogonadotropic hypogonadism type 1. Androgen therapy with testosterone had been initiated for both siblings to induce secondary sexual features. Ptosis was reported by Reardon at 2007 in case series of 2 siblings with Kallmann syndrome. This was the only documented cases in literature to link ptosis to Kallmann syndrome. To our knowledge our case is the second to report this association. The presence of a family of three brothers with Kallman syndrome and the association with ptosis are unusual

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EP311

The comparison of nocturnal and fasting ghrelin concentration in children with growth hormone deficiency and with idiopathic short stature

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Introduction
Ghrelin - a growth hormone (GH) secretagogue - presents a circadian rhythm with higher nocturnal concentration (similar to GH). As daily ghrelin production depended on food intake and nutritional state, we decided to assess ghrelin concentration at 60th at 90th minute after falling asleep and at 6:00 am (after 12 hours of fasting), and compare the results to determine the differences between nocturnal and morning ghrelin release in short children, both with idiopathic short stature (ISS) and with growth hormone deficiency (GHD). We also decided to correlate nocturnal and morning ghrelin concentration with the nocturnal GH concentration, measured at the same time points, as well as with the insulin-like growth factor I (IGF-I) and the maximal GH concentration during stimulating tests.
Methods
In 19 short children (aged: 10.36±3.06 years), ghrelin and GH concentration at 60' and 90' after falling asleep, as well as fasting ghrelin and IGF-I concentrations were measured. Moreover, two GH-stimulating tests were performed to establish the diagnosis: ISS or GHD.
Results
A significant correlation was observed: a) positive-between nocturnal ghrelin (both at 60' and at 90') and fasting ghrelin concentrations; b) positive - between ghrelin at 60' and nocturnal GH concentrations (both at 60'and at 90') ; c) negative - between ghrelin at 60' and IGF-I concentrations; d) negative - between ghrelin concentrations at 60' and body mass index of children.
Conclusions
1. In short children, fasting ghrelin indirectly reflects its nocturnal concentration, however it is significantly higher than the nocturnal one.
2. Despite the fact that ghrelin appears to stimulate GH secretion at night, and IGF-I is the main peripheral mediator of GH activity, it appears that in short children the lower levels of IGF-I the higher nocturnal secretion of ghrelin. This indicates inadequate GH synthesis or effects on peripheral IGF-I production in these cases.
3. Additionally, a higher nutritional state is an independent factor which influences lower nocturnal ghrelin secretion.

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EP312

Multiple endocrine neoplasia 1, 4 or simple concomitance ?

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Introduction
The association between pituitary adenoma and hyperparathyroidism is the main feature of multiple endocrine neoplasia (MEN) 1 but also for a novel MEN4 syndrome. Germline mutations in the cyclin-dependent kinase (CDK) inhibitor 1b gene (CDKN1B) were identified in patients with MEN4. The most common phenotype of the 19 established cases of MEN4 that have been described since now is primary hyperparathyroidism (PHPT) followed by pituitary adenomas. There are a limited number of cases with MEN4 and that way the association between phenotype and genotype is very difficult in order to have a positive diagnosis.
Aim
Tto present the discovery in uncommon circumstances of multiple endocrine tumors in a patient with no signs or symptoms of endocrine disorders and the difficulty to classify a possible MEN 1 or 4 syndromes.
Case presentation
We report the case of a 74-year-old female without significant family history of endocrine disease who was discovered with pituitary tumor (12/9.5 mm) and right adrenal incidentaloma (34/19 mm) at CT scan. The medical history revealed the presence of hypertension and a hip fracture at the age of 60. The patient was overweight (BMI=26 kg/m^2) with no particular signs of endocrine dysfunctions. The endocrine panel taking into account both pituitary and adrenal tumors revealed GH nadir during OGGT=23.7 pg/ml, IGF1=456 ng/ml (64–188) with central thyroid insufficiency (TSH=0.027 µUI/ml, fT4=1.39 ng/dl) and normal values for: prolactine, ACTH, plasma cortisol, free urinary cortisol, 24-hour urinary fractionated metanephrines. The ultrasound of the neck area discovered the presence of multiple thyroid macronodules and o nodular lesion located posterior to the right thyroid lobe suggestive for parathyroid adenoma. High levels of parathyroid hormone (186.2 pg/ml), hypercalcemia (11.04 mg/dl) along with osteoporosis (distal forearm T-score=–3.1 S.D.) and normal values of vitamin D were consistent with the diagnosis of PHPT. The parathyroid 99mTc-MIBI scintigraphy revealed the presence of multiple adenomas in all four glands. Regarding the thyroid the level of calcitonine was normal also the fine needle aspiration biopsy. The patient declines the surgical treatment for GH secreting pituitary adenoma and also PHPT. Somatostatin analogues and close surveillance was the decision for this patient.
Conclusion
In the absence of genetic result of possible mutation is very difficult to decide the MEN type or to conclude for simple concomitance. The phenotype otherwise extremely suggestive for MEN is not enough for delimitation between the type 1 and 4.
Keywords: MEN1, MEN4, fenotype, genotype.
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EP313

Radiotherapy in acromegaly: a single centre experience
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Background
Radiotherapy (conventional and/or radiosurgery) is an effective treatment option in patients with acromegaly when biochemical control of the disease cannot be achieved by medication and/or surgery. Purpose: The aim of our study was to evaluate the efficacy of gamma-knife radiosurgery or conventional radiotherapy in the treatment of GH-secreting pituitary adenomas.
Materials and methods
We conducted a retrospective analysis of 22 acromegaly patients treated with gamma-knife radiosurgery (n=19), conventional radiotherapy (n=2) or both methods (n=1) between 1996 and 2018 at the University Hospital Centre Zagreb. The data were analysed to assess biochemical remission defined as low or normal IGF-1 without IGF-lowering medication. Results
The median follow-up (FU) was 63.5 months (range 14–192 months). A biochemical remission was achieved in 10 patients (45.4%) with the actuarial remission rates of 13.6%, 27.2%, 40.9% and 45.4% at 1, 2, 4 and 5.5 years, respectively. The median time to biochemical remission was 21 months (range 6–66). There were no statistically significant associations between patients age, gender, tumour volume, dose of radiation or duration of FU and biochemical remission. However, there was a trend to higher remission rate in patients with lower IGF-1 before radiotherapy (P=0.053). Tumour growth control was achieved in all patients. New hormone deficiencies were found in 9 patients (40.9%) (in 6 patients one and in 3 patients two or more hormone deficiencies). This corresponds to the incidence of one new case of hypopituitarism per 5.5 patient-years. Conclusions: Radiotherapy offers endocrine remission and tumour control in a substantial proportion of patients with GH-secreting adenomas. Given a high cost of life-long medical treatment and a moderate risk of hypopituitarism, radiotherapy of GH-secreting pituitary adenomas should be considered in all patients with residual tumour.
Keywords: acromegaly, radiotherapy, gamma-knife.
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EP314

Malabsorption of levothyroxine sodium tablet in a patient with neuroendocrine gastric tumor, follow-up
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Multiple dose adjustments can sometimes be inefficient in reaching eumetabolic state in patients with hypothyroidism treated by levothyroxine sodium tablets.
We report a case of 46-year-old female who has been on levothyroxine sodium tablet replacement therapy since 2004 without ever reaching eumetabolic state. As sellar MRI ruled out pituitary adenoma, investigation perform absorption test with 300 mg levothyroxine and test was positive in aspect of presence of selective levothyroxine malabsorption. Initial endoscopies revealed chronic atrophic gastritis without excluding possibility for tumor presence. Serum CgA level was 521 mg/l. The final third endoscopy was successful in detecting the gastric submucosal change, confirmed by endoscopic ultrasound as submucosal lesion no larger than 12 mm located in the upper part of anterior gastric wall. Histological analysis of biopsy specimen confirmed lesion to be neuroendocrine tumor–Carcinoid tumour ventriculi, Chromogranin A +, NSE+; synaptophhisin-, CK 7+with Ki67+in 2% tumour cell. Further imaging excluded its metastatic spreading, so the indication for surgical removal was established. Patient could not undergo surgery with TSH levels exceeding 100 mmU/l and free T4 lower than 5 pmol/l despite being on 300 mg of levothyroxine daily substitution regimen. Changing to a gel capsule formulation taken once a day at dose of 100 mg lead to a rapid TSH decreasement and thyroid hormones normalization, so the patient was surgically treated as eumetabolic. After six months, the patient had an unregulated thyroid status again (TSH 76.26 mIU/l, fT3 2. 7pmol/l, fT4 5, 1pmol/l). We did a control endoscopy and determined the level of gastrin (1432.0 pg/ml) and CgA (798 mg/l) and Gallium-68 Dotatate PET/CT scan thereafter (normal). We are now looking for Zollinger-Ellison syndrome and the patient is receiving 500 mg of levothyroxine sodium tablet.
This case suggests that gastric chronic inflammatory processes and neuroendocrine tumors as well may affect levothyroxine absorption.
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EP315

What we found the hidden cause of SIADH?
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A 74-year- old gentleman was found to be hyponatraemic when he returned from birds watch trip with cellulitis of lower legs. He was generally fit and well apart from hypertension for which he had been on Amlodipine and Irbesartan. He was admitted with severe hyponatremia in July 2019 and was diagnosed with idiopathic SIADH as evidence of low serum osmolality (252 mosm/kg), high urine sodium (41mmol/l) and high urine osmolality (657mmol/kg). His Amlodipine and Irbesartan were replaced with Doxazosin. His thyroid function and adrenal function were normal. Underlying causes such as malignancy were investigated by CT Head and CT CAP showing no apparent causes. His sodium was closely monitored in Ambulatory Clinic for 2 months by liaising with endocrine specialist. Demeclocycline was initiated as he struggled with fluid restriction and the dose was adjusted later. He was seen in the endocrine clinic for further management in view of poor response to Demeclocycline. He was unfortunately re-admitted under urology team with new presentation of urinary retention, haematuria, hesitancy and frequency. Per-rectal examination showed moderately enlarged prostate. He was treated as an obstructive uropathy with

immediate catheterization. CT abdomen and pelvis showed locally invasive prostate cancer causing left-sided hydronephrosis and hydroureter, with abdominopelvic lymphadenopathy and liver metastases. Urgent urology intervention was required to relieve obstructive uropathy. There was an unclear diagnosis between prostate cancer and rectal malignancy initially due to presence of liver metastasis and normal PSA level. Hence, MRI pelvis demonstrated the high clinical suspicious of prostate cancer with liver and bone metastasis. Flexible sigmoidoscopy and rectal biopsy excluded the rectal cancer. Giving that, normal PSA level, CT scan result and unknown cause of SIADH, Prostate biopsy was performed and confirmed the diagnosis of NET neuroendocrine tumour of prostate by showing the extensive infiltration of small cell neuroendocrine carcinoma comprising 95-100% of tumour burden. Immunohistochemistry revealed diffuse CD56 and synaptophysin positivity. There was diffuse TTF1 staining and negative PSA expression. Gut hormones profile was within normal limit.
Discussion
This case highlights the importance of investigating the underlying cause of malignancy in newly diagnosed SIADH without obvious cause. Moreover, normal level PSA does not exclude neuroendocrine tumour of prostate. Therefore, close monitoring and observation for new SIADH might reveal the underlying cause and avoid missing evolving malignancy?!

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EP316

Aggressive evolution of a neuroendocrine tumors of the lung (Lu-NETs) - case report

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Background
Lu-NETs are a heterogeneous family of neoplasms ranging from quite indolent lesions with extremely aggressive tumors with very poor prognosis. These neuroendocrine entities are further summarized into two groups according to their biological aggressiveness: Well-differentiated: carcinoids typical (G1) and atypical (G2).Poorly-differentiate: SCLC (Combined) and LCNEC (Combined) (G3). Alarm signal on the aggressive evolution of the SCLC
Case report
Female, 60- ys. old, consult the doctor for Atrial Fibrillation. Chest x-rays: lobar atelectasis top left. CT scan: 1. lobar atelectasis top left by total obstruction from the origin of left upper lobar. 2. Lymph node metastases in hill and mediastinum. Bronchial biopsy: tumor infiltrated with insular architecture, small cells, high nuclear/cytoplasm ratio partly free chromatin, big round nuclei, bizarre cell bodies=Small Cell Lung Neuroendocrine Carcinoma (SCLC). IHC: TTF1-intensely positive in tumor cells. Cromogranin intensely positive. Synaptofizin-positive. CK7-negative. Ki67–25%positive. Treatment: Chemotherapy+radiotherapy. After nine months CT abdomen: tumoral mass in left adrenal, possible MTS. After another two months: Carcinoid syndrome: flushing, diarrhea, bronchoconstriction, tachycardia episodes. Biochemical markers: neuron specific enolase- increased chromogranin A- slightly increased. Treatment: Sandostatin LAR 20 mg/28 days. After 14 months of the diagnostic, the patient dies with cerebral MTS.
Conclusions
SCLC, is a highly aggressive disease; a young woman, with no smoking history, with a short period of stabilization after the treatment, develops quickly brain MTS and dies in short time.

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EP317

Hypopituitarism and vitamin D deficiency in a patient with primary CD8+ T-cell deficiency.

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Introduction
CD8+ T-cell deficiency is a feature of many chronic autoimmune diseases. Its association with vitamin D deficiency was described and it has been suggested that vitamin d deficiency contribute to the increase of the incidence and the progression of autoimmune diseases.
Herein we report a case of hypopituitarism and vitamin D deficiency in a patient with CD8+ T-cell deficiency.
Observation
A 28-year-old woman was admitted for a severe hypocalcaemia. She was born at term to healthy consanguineous parents and had a history of a primary CD8+ T-cell deficiency diagnosed at the age of 2 years, recurrent infectious diseases, hepatic cirrhosis and a pathological fracture of the femoral neck. She presented with constipation, abdominal pain and numbness and a primary amenorrhea. On physical examination, she had a body weight of 37 kg, a body height of 128 cm, a blood pressure of 10/6 cm Hg, a female phenotype with a female external genitalia (Tanner stage: breast development: stage 3 and pubic hair: stage 1), a dysmorphic syndrome and small hands and feet. Trousseau and Chvostek signs were positive. Electrocardiograph showed allonged QT: QTc 477 ms. The funduscopic examination revealed retinitis pigmentosa. On routine blood tests, she had a corrected calcium level of 62 mg/l, a phosphorus level of 27 mg/l, a magnesium level of 12 mg/l, a creatinine level of 4 mg/l. Hormonal investigations revealed a high PTH level of 470 pg/ml, a low 25 OH vitamin d level of 9 µg/l, a corticotropin deficiency with a peak cortisol level in response to insulin induced hypoglycemia test of 12 µg/dl and a hypogonadotropic hypogonadism. Peak GH level in response to hypoglycemia test was 33 mUI/l. Prolactin level and thyroid function were normal. Pelvic ultrasonography showed hypoplastic uterus with no visualized ovaries. Pituitary magnetic resonance imaging was contraindicated in our patient because she had a foreign metal screw. The patient was treated with hydrocortisone, vitamin d and calcium gluconate.
Conclusion
We report an unusual case of hypopituitarism and vitamin D deficiency in a patient with a primary CD8+ T-cell deficiency. It is difficult to assess the relationship between these disorders. Further investigations are needed to understand this association.

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EP318

Silent corticotropic adenoma revealed by headache

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Introduction
Silent corticotropic adenoma (SCA) is defined by the absence of clinical manifestations of Cushing’s disease despite the presence of ACTH and/or its precursors in tumor cells. It is a rare entity that represents 10% of pituitary tumors. It is known for its increasing expansion. Its clinical presentation is dominated by symptoms of tumor mass effect. We report the case of a silent corticotropic adenoma revealed by headache.
Case Report
67-year-old patient, not known to be diabetic or having hypertension; referred in our departement for post-operative monitoring of an operated pituitary macroadenoma. At clinical assessement, the patient complains of retro-orbital headaches with a decrease in visual acuity, without any signs of insufficiency or pituitary hypesecretion. A pituitary magnetic resonance imaging (MRI) is performed, showing a sellar and supra-sellar mass of $35 \times 29 \times 24$ mm in diameter. The surgical indication was retained. The patient was operated on 3 times. The histological study confirms the diagnostic hypothesis of a corticotropic pituitary adenoma. Postoperatively, the patient developed gonadotropic and thyreotropic insufficiency. A substitution with Levothyroxine at 25 µg per day is instituted. The other ante- pituitary functions are normal with a prolactin level and a cortisoluria of 24 hours in the norms; while MRI monitoring showed the persistence of the sellar and suprasellar tumor process measuring $40 \times 37 \times 22$ mm enhanced by contrast, with compression of the optic chiasm and the pituitary stalk and invasion of the right cavernous sinus. Currently, she is a candidate for surgery once again.
Discussion and conclusion
In summary, SCA is a distinct and aggressive subtype of pituitary adenomas. Preoperatively, they can be in the form of non-functioning pituitary adenomas and must be closely monitored postoperatively for the development of hypopituitarism, frequent recurrences, and more rarely for possible transformation into Cusching disease. Multimodal therapy may be necessary to adequately manage patients in whom the disease recurs, and larger clinical trials will hopefully demonstrate more effective drugs.

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EP319

Endocrine pathology hidden by IUD

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Introduction
Amenorrhea is a condition resulting from dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina. Hyperprolactinemia is a relatively common endocrine disorder that produces amenorrhea by suppressing hypothalamic GnRH secretion. We describe a patient who had a Levonorgestrel intrauterine device (UID) since 5 years and who presented with amenorrhea in association with a macroprolactinoma.
Case Report
A 45 year- old -woman presented for a routine gynecologic control. She had amenorrhea since an IUD was placed 5 years earlier. A routine blood test ordered by her gynecologist showed severe hyperprolactinemia (PRL 3298 microgram/l (4.8–23.3), accompanied by hypogonadotropic hypogonadism and hypothyroidism. IGF-1, ACTH and cortisol were normal. She was referred for further work up. She didn't complain of headaches, visual disturbances or galactorrhea. On physical examination galactorrhea was found. The visual field was impaired, with superior left temporal hemianopsia. Additionally, a pituitary MRI scan showed a pituitary tumor with supra-seller extension (30 × 19× 25 mm) and compression of the left side of the chiasma opticum and deviation of the pituitary cleft to the right. Moreover a voluminous cavernoma lokated parietal paraventricul left with discrete mass effect on the corpus callosum was observed. Bone mineral density was normal. Treatment was initiated with 0.5 mg cabergoline 3 times a week and L-thyroxine. The monthly PRL concentration dropped as following to 568, 208, 52.9 (bioactive 43) and 31.1 (bioactive 27) ng/ml respectively. 6 months and 12 months later the prolactin bioactive was 27.8 and 9.5, respectively. Control MRI 1 year later showed regression (13 × 7mm) of the macro adenoma with lateralization to the left.
Discussion
The clinical manifestations of hyperproleactinemia in premenopausal women are oligo-or amenorrhea and infertility and are correlated with the magnitude of hyperprolactinemia. Less often galactorrhea occurs. Hyperprolactinemia accounts for 10 to 20% of cases of amenorrhea. Our patient presented with amenorrhea in association with a pituitary macroprolactinoma. Cabergoline treatment was effective in PRL normalization and regression of the macroprolactinoma. In this case, in the past, it was thought her amenorrhea was due to her hormonal IUD and hyperprolactinemia was not considered as a possible cause of amenorrhea and therefore had not been detected. Moreover, she had no other associated symptoms.
Conclusion
Clinicians should be aware that the amenorrhea associated with the IUD can hide a prolactinoma. Serum prolactin should be measured in every woman with amenorrhea.

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EP320

Lateralized sixth cranial nerve palsy after inferior petrosal sinus sampling

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Introduction
Inferior petrosal sinus sampling (IPSS) is the gold standard test to differentiate Cushing's disease from ectopic Cushing syndrome. IPSS may cause severe complications; however, overall rates are low. Subarachnoid hemorrhage (SAH) has been rarely reported after IPSS. Here we report a case who developed hypertensive emergency, left 6th cranial nerve palsy, and SAH after IPSS.
Case
A sixty-two years-old female patient had a history of hypertension, ischemic cerebrovascular incident, coronary artery disease, and atrial fibrillation. She was diagnosed with bilateral adrenal incidentalomas five years ago, a right-sided 20 × 13 mm and a left-sided 40 × 40 mm adenoma. She did not exhibit typical features of Cushing syndrome but had high levels of salivary and 24-hour urinary cortisol. Serum cortisol was not suppressed with low dose dexamethasone (DXM). High dose DXM testing demonstrated less than 50% suppression. Adrenal venous sampling was unsuccessful. Left adrenalectomy was performed. Pathology showed nodular hyperplasia. The laboratory evidence of hypercortisolism vanished after surgery. Her follow-up was unremarkable until 2019 when she suddenly started experiencing hypertensive episodes. The evaluation revealed biochemically recurrent Cushing. ACTH was not suppressed but was in the gray zone and increased after CRH. High dose DXM testing suggested Cushing Disease. Hypophyseal magnetic resonance imaging (MRI) revealed a right-sided 4 mm adenoma. IPSS was planned. She was on apixaban, which was switched enoxaparin. There was no technical problem during IPSS. About an hour after the procedure, she developed acutely elevated hypertension (180/100 mmHg), headache, and vomiting. Her Glasgow-coma scale point was 15, without any deficits. Her blood pressure (BP) could not be controlled with oral medication; she was transferred to the ICU for intravenous nitrate infusions. Four hours following the procedure, her BP was still uncontrolled, and she developed a left-sided 6th cranial nerve palsy without any visual disturbances. A head scan revealed widespread hyperdensities in the subarachnoid space and ventricles. Her BP treatment was intensified with subsequent successful control. Cranial MRI excluded acute cerebrovascular incident. Her symptoms gradually improved. Nerve palsy dissolved after 48 hours. Follow-up imaging on the fourth day showed that hyperdensities had entirely resolved. She was discharged without any sequel. IPSS results were lateralized to the adenoma side. She is planned for surgery.
Conclusion
Hypertensive emergency and SAH after IPSS are rare but not unexpected. To our knowledge, this is the first case of transient 6th nerve palsy after IPSS. Physicians should be prepared for these uncommon presentations after IPSS.

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EP321

Infundibulo-hypophisitis with other metabolic disorders

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Introduction
Infundibulo - hypophisitis is a rare type neuroendocrine disorder characterized by autoimmune inflammation and various pituitary disfunction. It currently has no clear diagnosis criteria.We present the 26 years–old women, first diagnosed with infundibular neurohypophisitis with clinical Diabetes Insipidus and later with other metabolic disorders.
Case description
The patient, female, 26 years old came in the emergency room with extreme fatigue, weakness, alteration of the conscience and high fever. She was first diagnosed with Limfocitar Hypophysitis in 2017, secondary Diabetes Insipidus and pituitary hypothyroidism and was being treated with Desmopresin, Levothyroxine and Dexamethasone.At the moment of the presentation, she had the following parameters: Glicemia 1062 mg/dl, Urea 126 mg/dl, Creatinine 2.0 mg/dl, Na 155 mmol/l and K 3.6 mmol/l. HbA1C 9.4% Brain CT showed no acute cerebral damages. She was first hospitalized in Intensive Care Unit and later transferred in our Department as Secondary Diabetes Mellitus and hyperosmolar hyperglycemic state. During her stay, she complained of high fever and pain in both knees. She was diagnosed with Bilateral Pneumonia, Urinary tract infection and Tendinitis for which she was administered antibiotics and non steroid anti inflammatory drugs. Her blood glucose level was rapidly normalized and although she started insulin, after a few days she didn't required anymore therapy with hypoglicemiant drugs. Dexamethasone was gradually substituted with hydrocortisone as morning blood cortisol was 0.25 ng/ml (55–230). Other parameters resulted as followed: Urinary density 1010, CRP 15.4 (1.1–8.0 ng/ml), Triglycerides 649 mg/dl and Cholesterol 336 mg/dl. A total body scan was done which resulted normal. When discharged, her parameters were stable and she was given therapy with hydrocortisone, levothyroxine, desmopresine and fibrate.
Conclusion
Infundibulo- Hypophysitis is a rare form of neurological disorder. It can show both local symptoms of inflammation and hormonal dysfunction, depending on the location and dimension of the lesion. Anti inflammatory treatment and partial or total hypopituatarism can create metabolic disorders which need a closer look and a careful follow up.

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Heart failure as a first manifestation of acromegaly - A case report

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Acromegaly is a rare disease, which is mainly caused by benign tumour of the pituitary gland. Long-term presence of elevated growth hormone (GH) and insulin like growth factor 1 (IGF-1) levels accompanying this disease is associated with rheumatologic, cardiovascular, pulmonary and metabolic complications. Cardiovascular complications of acromegaly include a cardiomyopathy, arterial hypertension, arrhytmias, valvulopathy as well as endothelial dysfunction. Cardiovascular diseases are the leading cause of mortality in patients with acromegaly. We describe a 39-year-old male with undiagnosed acromegaly presented with acute heart failure caused by acromegalic cardiomyopathy. Pacient with 3 months history of artrerial hypertension was admitted to the department of internal medicine with orthopnea and pitting edema of the lower limbs experienced over a 1-month period. He also had excessive sweating over a 1 year. Physical examination on admission showed that his height and body weight were 193 cm and 150 kg. Blood pressure was 140/95 mmHg, and heart rate was 66/ min with sinus rhythm. He showed acromegalic features such as outstanding jaw and eyebrow area, enlarged hands, feet and also nose, tongue and lips. Pulmonary auscultation revealed coarse crackles in the bilateral lower lobes. Echocardiography showed dilated and hypertrophic left and right ventricles (IVS 17 mm), restrictive filling pattern, global hypokinesia, systolic dysfunction with EF 22% without valvulopathy. Comprehensive treatment of heart failure was initiated. To rule out coronary artery disease, a coronary angiography was performed without significant stenosis of coronary arteries. Laboratory tests revealed high level of GH which was not suppressed after glucose administration, high level of IGF-1. A magnetic resonance imaging scan revealed a 14 × 14 × 12 mm macroadenoma involving the pituitary gland. A diagnosis of acromegaly was established. Treatment by somatostatin analogues was initiated at dose 120 mg every 28 days. Control magnetic resonance imaging of the sella demonstrated a decrease of macroadenoma size (13 × 11 × 12 mm). Control echocardiography after 1 year of treatment showed improvement of left ventricle systolic and diastolic function (EF 33%). Nowadays trans-sphenoidal resection of macroadenoma is in the plan

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EP323

Association of an empty sella and grave's disease in a patient with acromegaly

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Introduction
Acromegaly is, in most cases, caused by growth hormone (GH) -secreting pituitary adenomas that lead to characteristic phenotypical changes. Its association with emty sella (ES) has been described and different theories has been given to explain such situation. Moreover, patients with acromegaly often develops different pathologies of the thyroid gland, however, the occurrence of grave's disease (GD) is quite a rare situation. Here we report a case of a patient diagnosed with grave's disease and acromegaly which was caused by a GH secreting adenoma and associated to an ES.
Case report
A 64-year-old female patient was referred for investigation of recent diabetes mellitus imbalance. For her personal medical history, she has been treated for hypertension and sleep apnea for 17 years now, and was operated for gonarthrosis and carpal tunnel syndrome in both hands 15 years ago. Regarding her family history, her first daughter was diagnosed with GD and the second daughter was followed for hyper prolactinemia due to an empty pituitary sella. Clinically, she was complaining of thermophobia, trembling, polyuro-polydipsic syndrome and weight loss. On examination, she had facial features of acromegaly with enlargement of her hands and feet and a goiter. Her blood pressure was often high. Biochemical testing revealed an elevated insulin-like growth factor-1 and a suppressed thyroid stimulation hormone (TSH) with positive anti-TSH-receptor antibodies. A pituitary Magnetic resonance imaging was performed, revealing an 11-mm adenoma with empty sella and no signs of local invasion. No history of pituitary apoplexy was described by the patient. A transphenoidal surgery was successfully performed and the diagnosis of GH-producing adenoma was also confirmed with immunohistochemistry. For her hyperthyroidism, she was treated with anti-thyroid drugs with a fast remission after 4 months of treatment.
Conclusion
The occurrence of an ES with a pituitary microadenoma has been described in many cases in literature; however its association with a macroadenoma is quite rare. One of the multiple physiopathological theories would be a paracrine effect of the growth hormone on the sellar bone. Moreover the combination of GD and acromegaly is not a commun situation, representing 1% of thyroid pathology in acromagalic patients.

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EP324

Significant weight loss as an unusual presentation of empty sella – case report

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Introduction
Unexplained weight loss is a cause for concern; it might indicate an underlying condition, usualy a catabolic state. In empty sella, the progressive loss of pituitary hormone secretion is usually a slow process, with symptoms varying from one person to another and depends on the underlying cause. Usually the weight remain relatively constant or we could have several arguments for weight gain.
Case report
A 57 years old man with significant weight loss–about 15 kg in the last 4 months, also associating marked physical asthenia, presented in our department to rule out an endocrine pathology, such as hyperthyroidism or primary adrenal insufficiency. All the symptoms had a sudden onset after the summer vacation and 2 weeks prior to presentation he acused musclular weekness and mialgia. The basic blood tests did not show anything wrong and he had no personal pathological background. The hormonal profile showed hypothyroxinemia with inappropriately TSH: FT4 = 0.5 ng/dl (*n* = 0.7–1.48), TSH = 4.49 micro UI/ml (*n* = 0.35–4.94) ; hypocortisolemia with low ACTH: plasma Cortisole = 1.23 microg/dl (*n* = 6.02-18.4), ACTH = 4.29 pg/ml (*n* = 7.2–63.3), low normal IGF1 level: 79.9 ng/ml (*n* = 36-200 for gender and sex), normal gonadotropic axis and normal prolactin level; the electrolytes level was normal. He also had a high level of anti-thyroperoxidase (ATPOs): 781 UI/ml (*n* <5.6), MRI of the pituitary gland was suggestive for empty sella. Substitutional treatment was established on corticotropic and thyrotropic lines, with the rapid disappearance of the symptomatology, the patient having no myalgia and gradually returning to the previous weight.
Looking for the cause of weight loss but also the explanation of empty sella syndrome, the patient also performed chest radiography and abodominopelvic ultrasound, the results being within normal limits–no sign of sarcoidosis or other granulomatous diseases, no tumor; he had no radiation or trauma, no infection and no sign of pituitary infarctisation. The presence of high ATPOs and partial hypopituitarism are suggestive for autoimmune hypophysitis.
Conclusion
Weight loss can be explained by secondary adrenal insufficiency and rarely by decreased intestinal absorption in hypothyroidism, but this is unusual and not significant in hypopituitarism. The symptomatology of our patient was suggestive of adrenal insufficiency, but the diagnosis of empty sella was a surprise. However, evolution of empty sella may be long-lasting and gradual, and rapid weight loss may be due to decompensation.

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EP325

Screening for developmental neurotoxicity test using 46C cells

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Developmental toxicity tests have been made by embryonic stem cell tests at the European Centre for the Validation of Alternative Methods or by embryonic body test in our laboratory. However, no neuronal-specific developmental toxicity test has been made yet. Therefore, this study was carried out using a 46C cell line, mouse embryonic stem cells with an endogenous Sox1-GFP reporter, to exploit the developmental neurotoxicity test. The expression of Sox1, a marker for neural progenitor, can be detected by green fluorescence and the fluorescence density is a critical factor to achieve neuronal differentiation. 46C cells were treated for 24 hours with 5-fluorouracil, hydroxyurea, chlorpyrifos, clioquinol, diazinon, nicotine and lead acetate as developmental neurotoxicants, or saccharin, sodium bicarbonate, sodium gluconate, and penicillin G as non-neurotoxicants. CCK-8 assays were performed to determine IC50 values after 48 hours of chemical treatment. The fluorescence intensity of GFP was measured after 4 days of treatment with cells using an automated digital microscope. Through CCK-8 assay, IC50 values of developmental neurotoxicant chemicals were obtained, whereas non-neurotoxicant chemicals showed low effects. In addition, the fluorescence intensity of GFP was not decreased with non-neurotoxicants. However, neurotoxicants decreased the fluorescence intensity of GFP at higher concentrations. This decrease of fluorescence intensity indicates that the neuronal differentiation of 46C cells is inhibited by the chemicals. Taken together, this study produced a model of the developmental neurotoxicity tests used embryonic stem cells that may use to evaluate the toxicity of new chemicals or new candidate drugs.

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EP326

Therapeutic difficulties in the management of craniopharyngioma

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The craniopharyngioma is a benign tumor, curable but aggressive by its localization involving the vital and visual prognosis of the patients. Treated mainly by surgery associated with radiotherapy which allows high long-term survival but at the expense of significant side effects, it nevertheless poses a problem of therapeutic management. The aim of this study is to illustrate the therapeutic difficulties in the management of craniopharyngioma
Patients and methods
13 cases of craniopharyngiomas confirmed by hormonal and radiological investigations (cerebral CT and MRI of the pituitary region) are collected.
Results
Average age at diagnosis is 25, sex ratio: 1.6. The revealing symptoms of craniopharyngioma are mainly represented by the visual disturbances found in 38% of patients, headache in 30%, diabetes insipidus in 15%. Somatotropic insufficiency was found in 30% of the patients evaluated, gonadotropic insufficiency in 38%, corticotropic insufficiency in 53% and thyrotropic insufficiency in 53%; as for diabetes insipidus, 53% of patients suffer from it at the time of diagnosis The average size of the tumor varies from 19 to 29 mm. Therapeutically, 53% of patients underwent surgery, 3 patients received an injection of yttrium and 2 patients underwent a stereotaxic puncture. 2 ventriculoperitoneal leads have been put in place for the treatment of hydrocephalus. Simple monitoring is recommended in a patient. The postoperative morbidities are: 2 cases of diabetes insipidus, one case of breach with fever and a corticotropic deficit.
Discussion
The initial management of craniopharyngiomas depends on the clinical presentation. Signs of intracranial hypertension as well as progressive visual impairment require urgent neurosurgical treatment for hydrocephalus and/or decompression of the cystic portion or tumor. Craniopharyngioma surgery aims to have as much surgical excision as possible to remove as much of the tumor as possible and to decrease the rate of local recurrence. However, this extensive surgery is complicated by a high rate of mortality and morbidity without preventing a significant risk of recurrence since it can reach 62% at 10 years. Recurrences are one of the most common complications, thus posing management difficulties, Conventional radiotherapy being the elective treatment at this stage. Chemotherapy by injection of bleomycin and interferon alpha is reserved for cystic forms.
Conclusion
The management of craniopharyngioma requires multidisciplinary cooperation. Surgery remains the main treatment. The surgical intervention must attempt an optimal tumor reduction while respecting the integrity of the optical and hypothalamic structures. Early diagnosis remains the determining factor in prognosis

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EP327

Conservative management of pituitary apoplexy – a case series

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Introduction
Pituitary apoplexy is a rare complication in 2%-12% of pituitary adenomas, due to sudden hemorrhage or infarction. Patients with signs of meningeal irritation, important visual field defects, ocular paresis, decreased unilateral or bilateral visual acuity or altered consciousness are treated by neurosurgical intervention, while patients without these signs could be managed conservatively.
Aim
To present a series of 4 cases with pituitary apoplexy managed conservatively.
Patients
4 patients (3 men and one woman), median age 38 years at diagnosis (range 36–65) were retrospectively reviewed. There were one patient with nonfunctioning pituitary adenoma (NFA), one with acromegaly, one with macroprolactinoma and one with Cushing's disease. There were 2 microadenomas and 2 macroadenomas (median tumor diameter 11.5 mm, range 6–41 mm). All patients but one were previously diagnosed with pituitary adenoma. No precipitating factors were identified.
Methods
FSH, LH, estradiol/testosterone, IGF1, TSH, FT4, serum cortisol and plasma ACTH, PRL were measured by chemiluminescence. Pituitary MRI and visual field assessment were performed.
Results
All patients presented with severe headaches and two patients showed ocular palsies. Signs of meningeal irritation, impaired visual field, decreased visual acuity or altered consciousness were not present in any patient. Panhypopituitarism was present in two patients. Transient aggravation of hypercortisolism was noticed in the patient with Cushing's disease, with hyperglycemia and hypokalemia. Serum natremia was normal in all patients. Conservative approach was decided in multidisciplinary team including endocrinologist, neurosurgeon, ophthalmologist and radiologist. Steroid therapy was administered. The outcome was favorable in all patients: remission of headaches and oculomotor palsies, improvement of cortisol and GH excess in patients with Cushing's disease and acromegaly, respectively. Tumor shrinkage was noticed in all cases.
Conclusion
In selected cases, without altered consciousness and absent or mild neuro-ophthalmic syndrome, conservative management could be an option for patients with pituitary apoplexy.

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Radiation therapy in the management of pituitary adenomas

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Despite advances in neurosurgical techniques, due to their size and their readily invasive nature, surgical resection of functional or non-functional pituitary macroadenomas is often only partial, justifying the use of any additional treatment (resumption of surgery, radiotherapy, treatment drug).
Patients and methods
10 patients were included in the study (7 men middle-aged 56 and 3 women middle-aged 48). 4 patients followed for non-functional pituitary adenomas and 6 for somatotropic adenomas. All patients received conventional radiotherapy (average dose 46.2 Grays) combined with drug treatment. The mode of discovery was either a cranial tumor syndrome (for non-secreting adenomas) or a dysmorphic acquired acromegaly syndrome (for somatotropic adenomas) radiotherapy combined with medical treatment has made it possible to normalize hormone secretion (GH and IGF1) in all patients with acromegaly and tumor reduction in 70% of cases and stabilization in 30% of cases. Regarding post radiotherapy complications are marked by the installation of anterior pituitary insufficiency in all cases within a variable period ranging from 1 to 3 years. The other complications (radionecrosis, stroke, radio-induced tumors) were not seen in this series.
Discussion
All studies find stabilization or a decrease in tumor volume in the majority of cases treated by conventional radiotherapy. The issue of routine radiation therapy after incomplete surgery for a non-secreting adenoma has long been debated. Success of radiation therapy in controlling tumor growth is high, 90–100% in most series, regardless of radiation technique and adenoma subtype. Success in achieving hormonal normalization in secretory tumors is more variable because of differences in patient population, radiation technique, and doses employed and variation of the definition of success. Complete biochemical remission is generally achieved in 50% of patients at 10 yr after treatment for most adenomas. Higher rates of normalization can be achieved with additional medical therapy. Hypopituitarism is an expectant result of radiation therapy. Overall rate of other treatment-related adverse effects is low. Radiation therapy should be considered in the management of patients with pituitary adenomas, particularly when medical and surgical options have been exhausted. Because response evolves slowly over many years and because hypopituitarism is likely to occur, patients should be counseled on the importance of continued endocrinological surveillance and medical management.
Conclusion
Radiation therapy retains a place in the therapeutic arsenal of pituitary adenomas, however in case of hypersecretion the period of effectiveness is a problem because it justifies another antisecretory therapy in the meantime.

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A rare tumor at the adult of the hypophysis: Atipic teratoid rabdoid tumor

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Pituitary adenomas are the most common cause of pituitary lesions. Atypical teratoid rhabdoid tumors are rare aggressive tumors of the central nervous system and are generally seen in children younger than 2 years of age, but also rarely in adults. Only 18 cases have been reported with pituitary involvement to 2018. Median survival in these tumors in adults is 21 months and the cause of death is usually tumor recurrence or leptomeningeal spread. Although surgery, chemotherapy and radiotherapy are used in treatment, a standardized treatment scheme has not been established for adults yet. A fifty-five-year-old woman presented to the hospital for a headache that started about 1 month ago. The patient also had a complaint of visual impairment that started 10 days ago. There was no additional problem in the patient's history, except for the diagnosis of diabetes mellitus, which started 1.5 years ago and regulated with metformin. On physical examination, visual acuity was decreased in both eyes with limited vision and looking down. In pituitary MRI, partial bleeding macroadenoma with 4 × 3 × 3 cm diameter filling the sellae, infiltrating the stalk and left cavernous sinus, filling the tuberculum sella, prepontine cystern and suprasellar cysternia were seen. The patient was found to have total pituitary insufficiency. She was given the operation with hydrocortisone and L-thyroxine treatment. Pathology: Macroscopically, approximately 3 cc volume tissue were examined. In microscopic sections, cellular undifferentiated tumor cells with narrow cytoplasm, vesicular nuclei, prominent nucleoli showing solid growth were seen. Necrosis and frequent mitosis were observed. Normal pituitary tissue was not seen. In immunohistochemical examination, GFAP, NSE, lymphoid (CD3, CD20, CD30), germ cell (PLAP), hormonal (LH, FSH, GH, TSH, ACTH) markers were negative. Epithelial markers (EMA, LMWK, pankeratin) were observed with focal staining and INI1 was lost. Ki67 proliferation index was found high (50%) in accordance with the mitotic index. These findings were reported as atypical teratoid rhabdoid tumor. In the PET/CT examination performed on the 15th day after the operation, a massive lesion with an intense pathological increase of SUV max. The patient was started on postoperative radiotherapy and the treatment of the vincrist, but despite this treatment, her vision disappeared in the following period, her consciousness gradually decreased. The patient died later. Atypical teratoid rhabdoid tumors of pituitary are rarely seen. they are resistant to treatment and can cause mortality by showing rapid progression.

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Panhypopituitarism as first manifestation in metastatic lung cancer

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Introduction
Metastases in pituitary gland are extremely rare with a reported prevalence of 1% among all pituitary tumor resections and 1 to 3.6% among post-mortem studies (1). Breast and lung cancer are the most common sites of primary tumor that have been reported to metastasize in pituitary gland and about 7% of all metastases are symptomatic (2.3).
Case report
A 62-year-old male with a 40-pack-year smoking history and no previous medical conditions presented with nausea, vomiting, fever, somnolence and a 6 kg weight loss in two weeks. Physical examination showed bradylalia, hypoacusis, drowsiness, tempo-spatial disorientation, fever (38 degrees Celsius) and an enlarged supraclavicular lymphatic nodule. No focal neurological deficits or meningeal irritation was found. Routine laboratory tests detected an elevated serum lipase (841 U/l), triglycerides (313 mg/dl), lactate dehydrogenase (994 U/l), creatinine (1.75 mg/dl), uric acid (10.69 mg/dl), c-reactive protein (10.9 mg/dl), fibrinogen (612 mg/dl), d-dimer test (1099 ng/ml), normal serum potassium and slightly elevated serum natrium (145.8 mmol/l). Additional, endocrinological work-up detected panhypopituitarism (FT4 = 4.8 pmol/l, TSH = 0.481 mIU/l, testosterone = 0.170 nmol/l, LH = 0.216 IU/l, cortisol = 47.9 nmol/l) and elevated prolactin levels (415.9 mUI/l). Proper substitutive hormone therapy was adopted. Hole body CT scan revealed the presence of a pituitary tumor, enlarged lymph nodes with necrotic areas in mediastinum and bilateral adrenal glands macroadenomas. Biopsy from supraclavicular lymphadenopathy, followed by pathological examination and immunohistochemistry uncovered a non-differentiated big cell neuroendocrine pulmonary carcinoma metastasis, staining positive for Thyroid Transcription factor 1, Synaptophysin, Chromogranin and Ki67 was positive in 90% of the tumoral cells. The patient condition deteriorated rapidly (obnubilation, tempo-spatial disorientation) with laboratory test showing elevated serum sodium and low potassium levels (Na = 159 mmol/l, K = 2.5 mmol/l). We suspected diabetes insipidus and antidiuretic hormone analogue therapy was started with a slightly improvement on patient condition and laboratory findings. Head MRI taken at three weeks after his initial admission revealed a pituitary tumor (31.4/30.6/27.5 mm) that exerted major compression on the third ventricle and determined internal hydrocephalus. The patient was relocated to neurosurgery department, where a ventriculoperitoneal shunt was placed. Unfortunately, the patient clinical condition continued to deteriorate despite correct treatment and after approximately five weeks after presentation, he passed away.

Conclusion
Panhypopituitarism and diabetes insipidus due to pituitary metastases represents a rare condition that highly complicates the diagnostic and management of patients with pulmonary carcinoma.

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EP331

GH deficiency in children with sickle cell anemia: About a case

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Introduction
Growth retardation in sickle cell children is common and multifactorial. Recent evidence suggests damage to the somatotropic axis. We report the case of a patient followed for homozygous sickle cell anemia and in whom we discover an associated GH deficiency.
Observation
It is a 13 year old child followed for homozygous sickle cell anemia, splenectomized for 2 years, not polytransfused. We were sent to the hematology department before a delay in weight gain with a delay in bone maturation (bone age=9 years). On examination, he was 139 cm <-2DS in height and 30 kg <3rd percentile in weight. The initial assessment showed a low IGF1 level, a correct nutritional balance and a negative celiac disease serology. Endocrine exploration was in favor of growth hormone deficiency (the GH peak on catapressan test was 6.51 ng/ml and the GH peak on insulin hypoglycemia test was 3.91 ng/ml). An associated corticotropic insufficiency was eliminated by a cortisol peak at 632.8 nmol/l (during the insulin hypoglycemia test) as well as a thyrotropic insufficiency (normal thyroid balance). The pituitary hypothalamic MRI was normal.
Discussion and conclusions
Systematic growth assessment is necessary in children with sickle cell disease as stunting (CR) is common and complex in this condition. Several factors are responsible for this: hematological state (anemia), endocrine function (GH deficiency, hypothyroidism), nutritional status (iron deficiency, vitamin B12 and folates) and bone state (necrosis of epiphyses bone) and hemochromatosis (if polytransfused child). Exploring CR in this population involves evaluating all of these parameters.

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Can you predict the recurrence of cushing's disease after surgery?

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Objective
Remission of Cushing's disease (CD) in the postoperative vary between 55–85%, recurrence of up to 25%. Remission and recurrence rates vary dependent on tumor size and neurosurgical expertise. The objective of this study is to describe whether there are clinical data that help us to predece recurrence of CD after transsphenoidal surgery (TSS).
Patients and methods
Retrospective analysis of patients who underwent as TSS for CD. Variables analyzed: age, sex, time to diagnosis, tumor size, serum cortisol, salivary cortisol, urinary-free cortisol (UFC). Recurrence was defined as disturbance of serum cortisol, salivary cortisol, UFC levels and ACTH in patients in remission after TSS.
Results
67 patients with CD treated with TSS. Women: 82.1%. Remission 71.6% (men: 3; women 45). Recurrence: 23.9% (men: 2; women 14).

	Recurrence	No recurrence	*P*
Age (years)	38.56±14.82	43.03±15.33	0.32
Time from onset of symptoms to diagnosis (months)	25±22.8	37.29±30.54	0.16
Time from diagnosis to surgery (months)	3.5±3.1	7.63±5.93	0.01
Tumor size (mm)	10.42±7.34	9.99±7.81	0.85
Basal cortisol presurgery (µg/dl)	25.21±13.63	22.9±8.53	0.47
Midnight plasma cortisol presurgery (µg/dl)	14.6±3.2	14.47±6.66	0.94
Midnight salivary cortisol presurgery (µg/dl)	0.2±0.11	3.05±7.06	0.11
24-hour urinary cortisol presurgery (µg/24 h)	571.03±407.35	592.31±766.73	0.91
ACTH presurgery (pg/ml)	91.26±62.91	76.72±2.38	0.34
Basal cortisol postsurgery (µg/dl)	5.64±5.47	4.79±6.6	0.65
Midnight salivary cortisol postsurgery (µg/dl)	0.33±0.24	0.17±0.1	0.02
ACTH postsurgery (pg/ml)	24.59±42.38	22.31±32.55	0.85

Conclusions
Patients with recurrence of CD had higher levels of midnight salivary cortisol postsurgery. Recurrence of CD is similar to that described in the literature.

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Pituitary metastasis from lung cancer: uncomon presentation

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Background
Pituitary gland metastasis is rarely the initial presentation of metastatic cancer. Most cases of pituitary gland metastasis are asymptomatic with diabetes insipidus being the most common symptomatic presentation. It can rarely present with symptoms of hormone underproduction such as anterior pituitary deficiency. Although pituitary gland metastasis is rare, it is underestimated, as it is commonly misdiagnosed with pituitary gland adenoma due to the lack of clear radiological criteria differentiating between both.
Case Report
We present a case of a 63-year-old male known as small cell lung cancer owner for already two years, under chemotherapy and mediastinal radiotherapy. The brain scanner initially done as assessment of extension didn't show any anomaly as for the rest computed tomography scan; however four months later; the patient presented blurry vision and persistent headache. This was followed by a brain magnetic resonance imaging (MRI), which showed one unique lesion with an enhancing mass 40 mm long axis involving the right clivus, intrasellar and suprasellar cistern with mass effect on the optic chiasm and involvement of the cavernous sinus and the internal carotid artery; this was supporting both diagnosis of pituitary's macroadenoma and pituitary gland metastasis of small cell lung cancer. Further workup showed no sign of hypersecretion; but conversely showed evidence of hypopituitarism like corticotroph deficiency with (morning cortisol level 36 nmol/l), thyreotropic deficiency TSH (0.062 uUI/ml) FT4 (10.19 pmol/l), gonadotropic deficiency FSH (0.403 mUI/ml) and LH (<0.100 mUI/ml) and disconnection hyperprolactinemia PRL (32 ng/ml), however there wasn't any sign of diabetes insipidus.

Conclusion
The majority of pituitary gland metastasis cases presenting with hypopituitarism have lung cancer as their primary tumor. Many cases of pituitary gland metastasis have been misdiagnosed as pituitary adenomas due to the lack of clear radiological findings that differentiate between these two conditions. However, it is important for physicians to be familiar with the radiological findings and presentations that could favor one diagnosis over the other.

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Optimal cumulative dose of cabergoline does not appear to cause fibrotic pulmonary side effects in prolactinoma

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Introduction
Dopamine agonists (DAs) consisting of cabergoline (CAB) or bromocriptine is the primary therapy in prolactinomas. DAs are also used in Parkinson's disease and restless leg syndrome with much higher doses. As a result of reports related to doses in these patients, it is known that long term use of DAs can lead to fibrotic syndromes affecting heart and lung. Cardiac valvulopathies are the most common investigated side effects but there are case reports of pleuropulmonary fibrosis. These reports raise concern for the safety of DAs in prolactinoma due to possible pulmonary side effects. Terefore we evaluated the pulmonary functions of prolactinoma patients receiving CAB treatment.
Patients and methods
Seventy three patients who received CAB for at least 18 months are included in the study. Chest X-ray and pulmonary functions like forced vital capacity (FVC), total lung capacity (TLC) measurements and diffusion capacity monitoring with carbon monoxide (DLCO; normal range: 80-100%) were performed at the last visit of each patient. Patients with a history of pulmonary disease and using drugs which may deteriorate pulmonary function are excluded from the study. Data of the patients are reviewed retrospectively. Cumulative dose of CAB and the total time of CAB usage are calculated. All patients were evaluated by a pulmonologist and those with abnormal results were requested additional tests like high resolution computerized tomography (HRCT) of the chest if needed.
Results
The study consisted of 34 male and 39 female with a mean age of 43 years (range 22–78). The mean cumulative CAB dose was 244 mg (range 24–1298) and the mean time of CAB use was 75 months (range 18–300). Mean values of FVC, TLC and DLCO were 104±14%, 102±12%, 95±16% respectively. Among 13 asymptomatic patients (17%) with abnormal DLCO results; 2 patients had significantly decreased DLCO (mean CAB cumulative doses; 120 and 175 mg) but physical examination and chest HRCT revealed no pathology, and the others had DLCO values just below the border but also with normal physical examination and chest X-ray findings. However, these abnormal DLCO results were not related to cumulative CAB dose in these patients ($P=0.6$).
Conclusion
CAB appears to be safe for pulmonary function with mean cumulative doses of 244 mg in prolactinoma patients. But as low DLCO could be the early finding of interstitial lung disease, evaluation of pulmonary functions and follow-up according to the results may be rational during long term treatment of prolactinoma with DAs.

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Complications of acromegaly regarding GH concentrations

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Introduction
Acromegaly is a rare disease caused by excess production of growth hormone (GH) and is associated with multiple complications. The prevalence of associated complications and the mortality rate are associated with the duration of exposure to elevated GH levels, early diagnosis being imperative. Diagnosis of acromegaly is most frequently late, after several years of evolution, with the development of cardiovascular, respiratory, metabolic complications. The presence of multiple complications in these patients contributes to an increased mortality/morbidity rate and a decreased quality of life.
Methods
The study group included 22 patients with acromegaly (women/men=15/7), aged 24 to 71 years (50.00±5.32). Patients were diagnosed and monitored at the Endocrinology Clinic in Timişoara between 2000 and present.
Results
The diagnosis was established late, 90.9% of patients had pituitary macroadenoma (preoperative adenoma dimension 25.43±12.50 mm) and 95% had complications of acromegaly at the time of diagnosis. The preoperative GH value was 21.54±25.51 ng/ml and the preoperative IGF-1 value was 666.57±346.10 ng/ml. The average number of years of illness in the studied group was 9.82±5.32 years. The studied group presented multiple complications of acromegaly. Frequency of complications presented in the group: 68.2% left ventricular hypertrophy, 54.5% sleep apnea syndrome, of which 13.6% had mild form, 13.6% had moderate form and 27.3% had severe form, 13.6% artrosic disease, 40.9% splenomegaly, 31.8% type II diabetes, 59.1% decreased glucose tolerance, 72.7% obesity, of which 31.8% grade I, 22.7% grade II and 18.2% grade III, and 8 out of 9 patients who had ophthalmological evaluation presented the narrowing of the visual field. We performed the Pearson correlation test of acromegaly complications with the preoperative GH and IGF-1 values and with the total duration in years of the disease, without statistically significant differences. The normalization of the hormonal parameters in the following years was accompanied by the improvement of the clinical picture and complications, with the improvement of the quality of life.
Conclusion
Early diagnosis and prompt assessment of acromegaly complications contribute to improving the quality of life, reducing complications and decreasing morbidity and mortality in acromegaly.

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GH-secreting adenoma in peripubertal period

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Introduction
Gigantism represents a rare pathology in children, characterized by growth hormone (GH) excess, before epiphyseal fusion. It associates significant morbidity and decreased life expectancy, in lack of appropriate treatment.
Case presentation
O.D., a male patient, 16 years old now, has been followed in our clinic since 2016, being diagnosed with gigantism in Bega Pediatric Clinic, at the age of 12 years 9 months. In 2014, the patient presented visual disturbances, headache, soft tissue swelling, accelerated growth in height (weight 85 kg, height 171 cm, S.D.=+ 2.6). Laboratory data confirmed high values of IGF-1 and basal GH, respectively non-suppressive GH at oral glucose tolerance test. No other pituitary insufficiency was noted. Pituitary MRI revealed a 3.9 cm pituitary macroadenoma. Transsphenoidal adenomectomy was performed, but only a part of the tumor could be removed (tumor remnant volume: 34/20/30 mm). Postoperatively, somatostatin analogue treatment was started. Later, due to the incomplete response (with persistent sleep apnea and headache), dopamine agonists (cabergoline) were added. In 2016 the patient was operated again, without complete removal of the tumor. In addition, partial pituitary insufficiency (on gonadotrophs and thyrotrophs) developed. Pituitary MRI shows a tumor remnant of 1.9 cm. Pegvisomant was added to somatostatin analogues and cabergoline treatment. In 2017, due to the persistence of symptomatology and the unsatisfactory response to the medical treatment, gamma-knife radiosurgery was performed. Also, the somatostatin analogue was changed. Up to now, the disease is well controlled under treatment.
Conclusion
Advances in the pharmacotherapy and radiosurgery in patients with acromegaly and gigantism allow successful control of the disease. Precocious

diagnosis is important, many of the complications being reversible in initial stages.

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EP337

The role of contrast-enhanced fast imaging employing steady - state acquisition (FIESTA) for postoperative residual tumor in pituitary adenoma

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Preoperative evaluation of pituitary macroadenoma tumor consistency is important for neurosurgery. Thus, we aimed to retrospectively assess the role of contrast-enhanced fast imaging employing steady - state acquisition (FIESTA) in predicting the tumor consistency of pituitary macroadenomas.
Objectives
In endoscopic endonasal transsphenoidal surgery of pituitary adenoma, after the removal of the lower component of the tumor, the upper component does not sag and the tumor may remain at the time of operation. We investigated whether residual tumor can be predicted from presurgical neuroimaging findings in pituitary macroadenoma retrospectively.
Subjects
Among the cases of pituitary adenomas mainly composed of solid components with a size exceeding 20 mm in which endonasal transsphenoidal surgery was performed from January 2008 to October 2019, we investigated the cases in which the residural tumor was observed in the postoperative magnetic resonance imaging (MRI) findings retrospectively.
Results
The subjects were 13 cases, 4 males and 9 females, and the median age was 72 years (39–88 years). It was difficult to predict the residural tumor after surgery from T1-weighted images, T2-weighted images, contrast-enhanced T1-weighted images, and apparent diffusion coefficiennt (ADC) map in MRI. In addition, contrast-enhanced FIESTA was performed in 12 cases. Five cases of the low signal intensity region in preoperative contrast-enhanced FIESTA almost coincided with the residual tumor. Four cases of the low signal intensity region in preoperative contrast-enhanced FIESTA partially coincided with the residual tumor. There was no correlation between both images in three cases.
Conclusion
The low signal intensity region with contrast-enhanced FIESTA is considered to be a finding suggesting the possibility of residual tumor in endoscopic nasal surgery in pituitary adenoma.

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Intracranial germinoma mimicking a pituitary macroadenoma

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Background
Intracranial Germ Cell Tumors (GCTs) are thought to originate from error of primordial germ cells migration during embryonic development, manifesting during first and second decade of life and accounts for 3-5% of all intracranial tumors.
Methods
We report a case of a 22-year-old patient who presented with progressive visual loss with polyuria and polydipsia, harboring an intracranial germ cell tumor.
Case Presentation
A 22 years old female presented initially to neurosurgery clinic and then referred to endocrine clinic, with history of a chronic worsening headache and recent onset visual blurring along with polyuria with polydipsia. On further inquiry she was found to have primary amenorrhea, easy fatiguability and failure of development of secondary sexual characteristics. There was no history of galactorrhea, hirsutism or any significant family history. On examination patient had bitemporal hemianopia with breast development at tanner stage II and pubic and axillary hair at tanner stage I. Her initial hormonal workup was suggestive of panhypopituitarism with diabetes insipidus. MRI Pituitary showed a seller mass with suprasellar extension inseparable from the pituitary stalk, so an initial impression of a pituitary macroadenoma vs a pituitary stalk tumor was made and patient underwent transsphenoidal surgery. The histopathology suggestive of a germinoma, a germ cell tumor and a rare cause of panhypopituitarism. She was stated on chemotherapy followed by radiotherapy, after which her tumor size has reduced significantly.
Conclusion
Pituitary stalk lesions are rare, and their definite diagnosis is challenging as different etiologies presents clinically and radiologically in a similar manner with tissue diagnosis being the gold standard.

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A case report: Pituitary granulomatosis with polyangiitis

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Introduction
Granulomatosis with polyangiitis (GPA) is a systemic vasculitis with necrotizing granulomatous inflammation. Any organ including the pituitary can be involved. Here we report a patient diagnosed with GPA who had nearly complete resolution of pituitary mass after cyclophosphamide and methylprednisolone treatment.
Case
46 year old female patient was admitted to the hospital after being examined by several departments for fever, severe headaches and sinusitis which she had for 2 months. Her inflammatory markers were high and she had cavities seen on her chest radiogram. Her cranial MRI showed a 12 mm-diameter adenoma of cystic and solid components at the right half of the adenohypophysis. Her hormone profile was remarkable except the prolactine [52.84 ng/ml (4.79–23.3)]. Anti-proteinase 3 antibody is also positive. She didn't have diabetes insipidus. Pulse methylprednisolone treatment was started, followed by daily methylprednisolone in decreasing doses. Monthly IV cyclophosphamide treatment was also started. 4 months later MRI showed nearly complete resolution of the adenoma and there can only be seen a microcystic focal area at the right upper side of the gland. Her hormones are remarkable including prolactine.
Conclusion
Pituitary masses can rarely be seen in GPA and our patient's mass resolved with cyclophosphamide and methylprednisolone treatment.

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EP340

The galant trial: a randomised placebo-controlled trial in patients with a gallium-68 dotatate pet positive, clinically non-functioning pituitary macroadenoma on the effect of lanreotide on tumour size

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Rationale
At present, there is no approved medical treatment for patients with clinically non-functioning pituitary adenoma. A number of open-label studies

suggest that treatment with somatostatin analogues may prevent tumour progression in selected patients. *In vivo* assessment of somatostatin receptor status using 68Ga-DOTATATE PET could help to select patients responsive to treatment.
Trial objective
To investigate the effect of the somatostatin analogue lanreotide as compared to placebo on tumour size in patients with a ^{68}Ga-DOTATATE PET-positive non-functioning pituitary macroadenoma (NFMA).
Design
The GALANT study is an investigator-initiated, multicentre, randomised, double-blind, placebo-controlled trial in adult patients with a suprasellar extending NFMA, either surgery-naïve or as postoperative remnant. Included patients undergo ^{68}Ga-DOTATATE PET/CT of the head and tracer uptake is assessed after coregistration with pituitary MRI. Forty-four patients with a ^{68}Ga-DOTATATE PET-positive NFMA are randomised in a 1:1 ratio between lanreotide 120 mg or placebo, both administered as subcutaneous injections every 28 days for 72 weeks. The primary outcome is the change in cranio-caudal tumour size after treatment assessed with pituitary MRI. Secondary outcomes are change in tumour volume, time to tumour progression, change in quality of life and number of adverse events. The study protocol has been approved by the medical research ethics committee of the Academic Medical Centre of the Amsterdam University Medical Centres and by the Dutch competent authority. Financial support is provided by Ipsen Farmaceutica BV.
Conclusion
The GALANT study is the first double-blind and placebo-controlled intervention trial in NFMA patients. Inclusion has been completed and results are expected in the second half of 2021. If lanreotide is effective in reducing or controlling tumour size, this would present an important new treatment option for NFMA patients.
Trial registration
EudraCT 2015–001234–22, registered 10 March 2015, and Netherlands Trial Register NL5136, registered 18 August 2015. Registration took place before start of recruitment.

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EP341

Long-term-follow-up of patients with gastric bypass surgery secondary to craniopharyngioma associated hypothalamic obesity

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Background
Patients being cured of craniopharyngioma (CP) often suffer from severe hypothalamic obesity due to tumor localization or therapeutic interventions, which has a major impact on increased mortality and reduced quality of life. Gastric bypass surgery (GBS) was suggested to be an effective therapeutic option for weight reduction in those patients. However, long-term changes in body weight and postsurgical complications are unknown.
Methods
5 patients with severe hypothalamic obesity being cured of CP, who underwent GBS, were included in a retrospective analysis (age: 20.8±4.4 years BMI: 47.3±7.7 kg/m^2). They were compared to a control group of patients with common obesity who underwent GBS, matched for preoperative age and BMI (age: 23.1±3.7 years BMI: 48.7±6.3 kg/m^2).
Results
Gastric bypass surgery led to a distinct weight loss after 1.5±1.1 years in both groups (CP: –44.0 kg±19.4, controls: –43.8 kg±14.1; P=0.176). However, in long term follow-up (6.1±2.9 years) weight regain was observed in 3 of 5 CP patients, 1 CP patient suffered from severe postsurgical malnutrition, whereas only 1 CP patient had a favorable long-term outcome comparable to controls (BMI at long-term follow-up: 42.2 kg/m^2±10.5 vs 31.2 kg/m^2±6.3). Postoperative complications requiring in-patient treatment were significantly more often in CP (CP: 4/5 (80%), controls: 5/24 (20%), P=0.022).
Conclusions
Despite promising results of weight reduction in the first years following GBS, long-term outcome is worse in patients suffering from hypothalamic obesity. Weight regain is more likely and the rate of severe postsurgical complications is higher in patients with CP compared to controls.

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EP342

Cushing's disease with negative mri: an overview of the experience of the endocrinology-diabetology-nutrition department of oujda's Mohammed-VI university hospital- morocco

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Introduction
Cushing's disease is caused by endogenous hypercotisolism, due to the hypersecretion of the adenocorticotropic hormone (ACTH) by an ACTH-secreting pituitary adenoma. However, some patients with Cushing's disease have no visible adenoma on MRI. The goal of this study is to review the clinical features, diagnosis and medical preparation of patients with Cushing's disease.
Material and methods
A retrospective study including 6 patients with Cushing's disease and a negative MRI in the Department of Endocrinology-Diabetology of Oujda's University Hospital.
Results
The mean age of the patients was 33.6 years with a female predominance. All of the patients showed clinical signs of hypercortisolism. Elevated midnight blood cortisol and 24-hour urinary free cortisol as well as non-suppression of cortisol during 1mg overnight dexamethasone suppression test were observed in all cases. 100% of the patients had an elevated ACTH value and responded to 8mg dexamethasone suppression test. The hypothalamic-pituitary MRI was normal in all cases. The decisions considering treatment for each patient were discussed over multidisciplinary meetings. Thus, all of the patients have undergone preoperative medical therapies: 50% of the patients were treated with Metopirone, and 50% with Ketoconazole. All patients had a bilateral adrenalectomy, with a successful recovery from hypercortisolism. No case of Nelson's syndrome has been registered thus far.
Discussion and conclusion
Inferior petrosal sinus sampling (IPSS), though being invasive, is the gold standard for establishing the pituitary origin of ACTH secretion in patients with negative MRI and help guide the neurosurgical exploration using the endonasal transsphenoidal approach. However, in developping countries such as ours, this option is not available. Bilateral adrenalectomy seems more reliable and efficient in our context, but requires lifelong glucocorticoid and mineralocorticoid replacement with an increased risk of Nelson's syndrome.

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EP343

Vitamin B12 deficiency associated with multiple endocrine neoplasia type 1: About a case

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a rare disease, defined as a tumor developing in at least two endocrine glands including the anterior pituitary gland, the parathyroid glands and the duodeno-pancreatic endocrine tissue. This is an inherited disorder. However, sporadic cases account for 8–14%. We here report a case of MEN1 revealed by vitamin B12 deficiency.
Observation
A 37-year-old young woman admitted to our department of Internal Medicine for macrocytic anemia. Physical examination was normal. The biological assessment showed a macrocytic anemia: hemoglobin: 7.4 g/dl, mean cell volume: 112.4 fl, hyperbilirubinemia: 42 µmol/l, transaminase elevation: 132 U/l. Thyroid analysis was normal, calcemia at 2.53mmol/l with elevated parathyroid hormone: 154 pg/ml (normal range: 10–65 ng/l). A vitamin B12 deficiency was diagnosed <50 pg/ml and the serum folate was normal. The oeso-gastro-fibroscopy showed gastric atrophy and a 6 mm nodule the biopsy examination after resection concluded of a neuroendocrine tumor. The thyroid ultrasound revealed an EU-TIRADS 3 nodule and a left parathyroid nodule measuring 11 × 5 mm. The assassement of chromgramine A was elevated: 150 mg/ml (normal <102 ng/ml) and the urine dosage of 5-hydroxyindolacetic acid (5HIAA) was normal: 24 µmol/24 h (normal <40 µmol/24 h). A thoraco-abdominal CT scan revealed hepatomegaly

at 21 cm and splenomegaly at 14.3 cm. Then, our patient was diagnosed with MEN1 associated with Biermer disease, she was treated with injection of vitamin B12 and she was proposed for removal oft he parathyroid nodule.
Conclusion
We report a case of a patient with who initially presented with vitamin B12 deficiency and. This case revealed the rare co-existence of MEN 1 with hyperparathyroïdism, which has rarely described in the literature. A thorough evaluation is necessary to avoid a delay in the correct diagnosis and treatment of the underlying conditions.

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EP344

Pancreatic neuroendocine tumors and pheochromocytoma in vonhippel lindau disease

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Introduction
VonHippel Lindau (VHL) disease is an autosomal dominant disorder, responsible of the occurrence of multiple endocrine and non-endocrine lesions. When it comes to this hereditary syndrom., pheochromocytoma and pancreatic neuroendocrine tumors (pNET) require special monitoring and an appropriate treatment, The object of this case report is to highlight the different clinical presentation of the same lesion in the same patient and the difficulties in decisions' making when it comes to therapeutic care.
Observation
We report a case of a 40-year-old female patient diagnosed with VHL disease 20 years ago. The first manifestation of this syndrome was a pheochromocytoma in the right adrenal gland which presented with severe hypertension at the time. Genetics tests revealed a miss sens mutation in codon 86 exon 1, which confirmed the disease. During follow up, the patient developed multiples lesions: two cerebellar hemangioblastoma, a medullary and a puituitary stalk hemangioblastoma and multiple pancreatic cysts. In the latest radiological imaging, a new tumor in the left adrenal gland and 2 pancreatic lesions suggesting a pNET were found. The first pancreatic lesion was a 3- cm tumor and the second one was 1.1 cm, located both in the head At the clinical examination, the patient was suffering of paresthesia and pain in both legs due to the growth of the medullary hemangioblastoma, her blood pressure was normal and she did not present any symptoms suggesting a fonctionnal NET. The biological exams showed an elevated 24-h urinary catecholamine levels confirming the pheochromocytoma. Surprisingly, the insulin level was high, even though the patient never presented symptoms of hypoglycemia. An octreoscan was performed and it confirmed the endocrine nature of the first pancreatic lesion. For the treatment, a surgical intervention of the medullary hemangioblastoma was rejected by the neurosurgeons due to the post operative risks on the patient. As for the pheochromocytoma, a partial tumor resection was initially proposed; however, the final decision was a total adrenalectomy, considering the possibility of recurrence of new tumors. And for the pancreas, we opted for a surgical resection of the 3- cm tumor, considering the size and the location of the mass.
Conclusion
Genetic syndrome such as VHL requires a special attention to the evolution of the different lesions. The object of the clinical surveillance will be to decide the proper timing and nature of interventions necessary, to improve early diagnosis and successful treatment of the malignancies.

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EP345

Recurrent abscesses as a rare, life-threatening clinical manifestation of Cushing disease

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Introduction
Cushing disease, as a state of chronic hypercortisolism, causes diverse, often nonspecific symptoms, possibly delaying the proper diagnosis.
Case report
A 59-year-old woman with the history of type 2 diabetes mellitus, hypertension, osteoporosis and multiannual history of recurrent hospitalizations because of life-threatening multi-sited soft tissue and muscle abscesses, was admitted to the Department of Internal Medicine and Metabolic Diseases due to symptoms of sepsis. A month before the patient was hospitalized in the Department of Surgery because of left buttock abscess. The CT scan revealed iliopsoas and both buttocks abscesses and enlarged left adrenal gland. On admission the patient was in bad condition, lying, requiring other's help to sit. Physical examination revealed cachexia, thick, atrophic skin with a number of small scars after cutaneous abrasions, excessive chin hair, poor dental condition with severe hypodontia, facial plethora, proximal muscle wasting, arms and legs swelling, deep left buttock abscess cavity. Laboratory tests showed considerably increased inflammatory markers, normocytic anemia, hypoproteinemia with hypoalbuminemia. Blood and abscess cavity swab cultures were positive for MSSA. An abdomen and pelvis CT revealed iliopsoas and both gluteal muscles abscesses and two left adrenal gland lesions (18×22 mm and 34×22 mm) with density characteristic for adenoma. A pituitary MRI showed a 6mm lesion, described as Rathke's cleft cyst or atypical microadenoma. The treatment included antibiotics, red blood cell transfusion, negative-pressure wound therapy of abscess cavity and rehabilitation, which led to significant improvement of the patient's state. We suspected Cushing's syndrome, however, due to the patient's serious condition the hormonal diagnostics was postponed. The patient was readmitted to our Department after 3 months in order to perform diagnostics towards Cushing syndrome. The patient was in better condition, without clinical or laboratory signs of inflammation. We observed an increased midnight cortisol, the lack of cortisol suppression in low-dose dexamethasone test and cortisol suppression in high-dose dexamethasone test. The ACTH concentration was 27.98 pg/ml. CRH test revealed over twofold increase in ACTH and cortisol level after stimulation. Hormonal tests indicated Cushing disease. At the Department of Neurosurgery the bilateral inferior petrosal sinus sampling was performed, confirming pituitary source of hypercortisolism. Afterwards, the patient underwent a successful transsphenoidal pituitary surgery. Currently the patient's condition is still improving, she requires hydrocortisone supplementation.
Conclusions
Presented case shows that recurrent infections should make physicians consider the possibility of Cushing syndrome. It proves that chronic hypercortisolism is destructive and can lead to advanced disability.

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EP346

The role of Octreotide in the treatment of acromegaly

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Acromegaly is a rare disorder with a high morbidity and mortality rate. The diagnosis is typically prolonged over time due to a slow and hidden development of the disease. Current medical therapy for the treatment of acromegaly involves the administration of somatostatin analogues that effectively suppress excess hormone secretion. The objective of this study was to investigate the efficacy of octreotide therapy in acromegalic. A total of 32 patients have been treated with Octreotide since May 2015 when the medicinal was included in the reimbursement scheme in Albania. All patients have been treated every 28 days with Octreotide LAR 30 mg/2 ml. The concentration of GH and IFG1 was measured at 0 months and every 6 months thereafter. Of the 32 patients 50% received the Octreotide treatment after both surgery and Radiosurgery, another 37.5% of the patients received Octreotide treatment After surgery alone, and the remaining 12.5% received an Octreotide-only treatment. The Octreotide treatment reduced the levels of GH by 60% (significance $P=0.0072$) and IGF-1 by 12.5% ($P=0.08$) compared to the same levels measured before the treatment. For 30% of the patients the treatment achieved to bring GH and IGF-1 within normal values, 58% of the patients showed significant improvement (GH and IGF-1 reduction of 20% or more) towards the normalization of the levels, and 12% of the patients resulted resistant to the treatment. In conclusion, from the 32 patient cases treated with Octreotide we report a relevant reduction of the values of GH and IGF-1. The reduction is observed by measuring and comparing these levels before and after the treatment with octreotide. The treatment with somatostatin analogues is still the chosen treatment for acromegalic patients.

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EP347

Behaviour of the long-term clinical and analytical characteristics of a series of cases with hypopituitarism

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Aim
To describe the clinical and analytical characteristics of patients with hypopituitarism in the Endocrinology Department.
Materials and methods
This was a descriptive, retrospective study with 70 patients diagnosed with hypopituitarism in the Endocrinology Department´s outpatient consultations with a follow-up of up to 44 years. The qualitative variables were expressed in frequencies and the quantitative variables showed a normal distribution expressed in means±S.D.
Results
Out of the 70 patients, 44.3% were women and 90% Spanish. The age at diagnosis was 42.94±21.79 years with an average follow-up of 11.79±10.56 years. The BMI mean was 28.56±5.04 kg/m^2; of which 42.1% were obese, 31.6% overweight and 26.3% normal weight. The most frequent cause was non-functioning macroadenoma surgery with 47.1%. The most prevalent hormonal deficits were TSH with 92.9%, ACTH 91.4%, FSH/LH 87.1%, GH/IGF-1 54.3%, and ADH 45.7%. The following means were observed in the last blood sample: Glucose 88.59±27.30 mg/dl; HbA1c 5.86±0.73%; Cholesterol 180.27±37.47 mg/dl; HDL 57.35±19.47 mg/dl; LDL 100.57±31.22 mg/dl; TAG 138.51±65.37 mg/dl; T4L 1.02±0.21 ng/dl; IGF1 99.40±58.39 ng/ml. Hydrocortisone daily mean was 21.09±6.93 mg, and a dosage of three times a day was 67.2%. The average dose of levothyroxine according to weight in subjects under 65 years was 1.30±0.32 mg/kg/day and in subjects 65 years or older 1.04±0.31 mg/kg/day. The number of drugs used as chronic treatment was 6.75±3.16. Regarding comorbidities, dyslipidemia was observed in 60% of patients, hypertension 37.1%, and diabetes mellitus 15.7%. Alterations in bone densitometry were observed in 42.8% (osteopenia 25.7% and osteoporosis 17.1%). The majority was asymptomatic (68.1%) in the last visit and 21.7% reported asthenia. After diagnosis, 54.3% had readmissions (24.3% more than 3 times). The mortality was 7.1%, being the most frequent oncologic cause.
Conclusions
Surgery on the selar area represents an important cause of hypopituitarism. Most of them had excess weight, dyslipidemia, and decreased bone mass. Mortality was mainly secondary to oncological causes.
Keywords: hypopituitarism, pituitary, adenoma.
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EP348

A rare cause of ectopic cushing syndrome: Prostate cancer

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Objective
To report a rare cause of ectopic adrenocorticotropic hormone (ACTH) secretion leading to Cushing syndrome.
Methods
We describe the clinical presentation and management of a case of Cushing syndrome attributable to ectopic ACTH secretion from small cell cancer of the prostate.
Results
In a 74-year-old man developed hypocalemia and heart failure. He was found to have severe hypokalemia (serum potassium, 2.37 mEq/l). Hormonal evaluation revealed a high serum cortisol level of 56.57 microg/dl and a high 24 hour-urine free cortisol excretion of 3218.5 microg/dl (reference range, 4.3 to 176), confirming the diagnosis of Cushing syndrome. A serum ACTH level was elevated at 416 pg/ml (reference range, 0 to 46). An overnight high-dose (8 mg orally) dexamethasone suppression test was positive (serum cortisol levels were 50.3 and 55.1 microg/dl before and after suppression, respectively), and magnetic resonance imaging of the pituitary gland disclosed no abnormalities. Thorax and abdomen CT for ectopic ACTH secreting tumor disclosed no abnormalities too. In PET CT scan, 18 FDG uptake was detected in prostate. Transurethral biopsy of the prostate showed features of small cell prostate cancer. A prostate biopsy specimen showed small cell prostate cancer with highly positive staining for ACTH. The tumor was found to be resectable, but he was in intensive care unit and orotracheal intubated. He was treated with ketoconazole 600 mg/day, which yielded good temporary control of his Cushing syndrome (serum cortisol level was 19.72 microg/dl and serum potasium level was 4.8 mmol/l). After diagnosis, he died 1 month later as a result of influenza pneumonia sepsis.
Conclusion
Ectopic ACTH secretion accounts for 10 to 20% of all causes of endogenous cushings syndrome and is usually associated with neuroendocrine tumors and small cell carcinoma of the lung (up to 50%).
Small cell prostate cancer is a rare subtype that can be associated with ectopic secretion of ACTH and severe Cushing syndrome. With this subtype of prostate cancer, Cushing syndrome should be considered and appropriately managed.
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EP349

Intravenous dexamethasone suppression test in cushing syndrome diagnosis: Three cases

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Introduction
Dexamethasone Suppression Test (DST) is a useful approach in diagnosis and differential diagnosis of Cushing Syndrome (CS) despite its limitations. One of the major limitations is the difficulty to provide standard suppression dose depending on the variability of gastrointestinal absorption. One solution is for this testing serum Dexamethasone levels or test it with intravenous (iv) Dexamethasone In this case, we examined 3 patients to whom we applied intravenous DST in our clinic in 2019.
Case1
The patient who underwent left surrenalectomy and two pituitary surgeries due to Cushing Syndrome was referred to us. The Pituitary gland was showed as a thin line at pituitary MRI. Abdominal MRI was normal. The Diurnal Rhythm was preserved. The 24-hour urine cortisol was normal. 1mg DST suppression wasn't detected. The patient had low st4 level (0.63) whe thought it might be because of intestinal edema-induced absorption disorder and whe did IV overnight DST. (1mg/st iv DXM infusion between 23:00 and 03.00) CS was not considered in the patient who have cortisol suppression.
Case2
A 49-year-old female patient who had weight gain complaint had central obesity and proximal muscle weakness. Her cortisol rhythm was impaired. Night saliva cortisol and 24-hour urine cortisol were normal. There were no 1mg DST, 2-day 2 mg DST, and 2-day 2 mg DST+CRH suppressions. A 7 × 8 mm nodular lesion was detected at Pituitary MRI. The patient with longterm diarrhea underwent IV DST considering that she might have absorption disorder. The 0 th-24 th-hour ACTH and cortisol values were used in diagnosis. The results were interpreted in favor of Cushing Syndrome (CS).
Case3
A 58-year-old female patient with surrenal adenoma didn't have 1 mg DST, 2-day 2 mg DST suppression. Her cortisol rhythm was preserved. The 24-hour urine cortisol and saliva cortisol were normal. The 0th-24th-hour ACTH and cortisol values were used in the diagnosis (1 mg/S.D × m infusion between 1100 h and 1500 h) Since there were no suppression in the cortisol levels, sub-clinical CS was considered.
Discussion:
There are limited studies on IV DST Test. There is no complete consensus on the application protocol and the diagnostic threshold value yet.
The efficiency of the IV DST Test was interpreted as an expected result because the two case both had gastrointestinal malabsorbsiyon. The third case, hadn't malabsorbsiyon. The serum dexamethasone levels couldn't be tested during oral DST was performed.
IV DST should be remember as patient with absorption disorders or use drugs that affect the dexamethasone metabolism.
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EP350

Case report: the combination of acromegaly, primary hyperparathyroidism and colon cancer

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Introduction
Acromegaly is a chronic disease caused by excess growth hormone (GH) release from an adenoma caused by somatotroph cells of pituitary gland.In acromegaly, it is known that the risk of thyroid and colon cancer is increased 8 and 4 times, respectively, compared to the normal population.Moderate hypercalcemia, due to vitaminD activation, is seen in acromegaly, but overt hypercalcemia, generally secondary to primary hyperparathyroidism, is rare. Combination of acromegaly and primary hyperparathyroidism, often related with MEN-1 (Multiple endocrine neoplasia-1), has been reported in few cases.In this study, we wanted to share a newly diagnosed acromegaly with diabetes mellitus, multinodular goiter, primary hyperparathyroidism, and colon cancer.
Case
A 60-year-old male with hypertension and coronary artery disease was referred to our endocrinology clinic because of supressed TSH (thyroid stimulating hormone) level.As a result of examinations, he had been diagnosed with diabetes mellitus, multinodular goiter, and primary hyperparathyroidism.Because of his enlarged hands, feet and acromegalic face IGF-1 (insulin-like growth factor-1) was evaluated.Due to high IGF-1 level, glucose growth hormone suppression test (GGHST) was performed.GH was not supressed, compatible with acromegaly.Pituitary magnetic resonance imaging (MRI) revealed 14 × 10 mm nodular lesion in inferior part of pituitary gland, no cavernous sinus and optic chiasm compression were observed. Thyroid USG (ultasonography) revealed diffuse hyperplasic thyroid gland, with multinodular goiter, and a 22.8 × 12.8 × 57.8 mm hypoechoic lesion, suggested parathyroid adenoma, adjacent to the right superior thyroid lobe. Thyroid scintigraphy revealed active multinodular lesions on the upper left lobe of the thyroid gland, and parathyroid scintigraphy showed activity retention in the area that fit the thyroid gland in the right upper-middle section that could be compatible with parathyroid pathology.Fine needle aspiration biopsy (FNAB) of recommended thyroid nodules were reported as benign and nondiagnostic.Bone mineral densitometry was compatible with osteopenia, nephrolithiasis was reported on abdomen USG.Due to co-existence of acromegaly and primary hyperparathyroidism, MEN-1 was evaluated, genetic test was normal.His colonoscopy revealed 3–4 cm ulcer in rectum, and the biopsy result was adenocarcinoma.The patient was evaluated in terms of current diagnoses, operation for acromegaly and primary hyperparathyroidism was planned, but since it was stated by the oncology department that the operation for colon cancer is a priority for patient survival, the operation for colon cancer was planned first.Lanreotide for acromegaly, zoledronic acid for primary hyperparathyroidism were given.Since the patient wanted to be operated in the another center, he was discharged to apply after the operation.
Conclusion
Acromegaly causes an increased morbidity and mortality with metabolic effects caused by GH over-secretion and the mass effect due to compression of the pituitary adenoma.In the course of acromegaly, patients should be examined appropriately for possible complications.Acromegalic cases with hypercalcemia should be evaluated for parathyroid adenoma and possible MEN-1-syndrome, although it is not common.

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Cardiovascular risk factors in acromegaly: comparison between successful surgery with medical treatment

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Introduction
Acromegaly is an insidious disease caused by chronic GH and IGF-I hypersecretion associated with increased morbidity and mortality, mostly from cardiovascular complications. The aim of this study is to compare cardiovascular risk factors, between patients with medical treatment vs cured.
Materials and methods
This is a retrospective study of 37 acromegalic patients, 21 well controlled with medical treatment (IGF-I within the normal range for age and sex) and 16 cured after successful surgery and/or radiotherapy. Studied cardiovascular risk factors are: BMI, glucose metabolism, dyslipemia and hypertension. Of those on medical treatment, 57% received depot somatostatin analog (SST), 5% pegvisomant, 5% cabergoline, and rest SST with cabergoline. No cardiovascular event was observed.
Results
There is no significant differences in age at diagnosis, GH and IGF-I levels, and current IGF-I index. There are more hypopituitarism in the cured group despite no differences in radiotherapy. The number of macroadenomas, patients with dyslipemia and basal glycemia disturbances are significantly higher in the "not cured" group, however there is no differences in diabetes mellitus.

	Curados	TTO Medico	*P*
Age	57.7	59.86	ns
Age at diagnosis	39.6	45	ns
Sex (F/M)	56.3/43.8	47.6/52.4	
Macro/Micro	75/25	90.5/9.5	$P<0.05$
Surgery	100%	81%	$P<0.05$
Radiotherapy	37.5%	33.3%	ns
Hypopituitarism	62.5%	42.9%	$P<0.05$
GH at diagnosis	22.5	21.3	ns
IGF-I at diagnosis	750.17	811.88	ns
IGF-I index at diagnosis	5.61	5.93	ns
Current IGF-I index	1.52	0.97	ns
BMI	27.47	28.7	ns
Hypertension	43.8%	38.1%	ns
Dyslipemia	50%	71.4%	$P<0.05$
Basal glycemia disturb	6.25%	23.8%	$P<0.05$
DM	18.8%	14.3%	ns

Conclusion
A good hormonal control can be achieved with current medical treatments. We demonstrated that cardiovascular risk is similar in both groups. Therefore, strict hormone control is required to improve the cardiovascular prognosis in patients with acromegalia.

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EP352

Hypercortisolism in a patient with previous medullary thyroid carcinoma–is it paraneoplastic or co-existent cushing's disease?

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Introduction
Medullary thyroid carcinoma (MTC) accounts for 3-9% of all thyroid cancers and only 0.7% develop paraneoplastic Cushing's syndrome. However, incidence of endogenous Cushing's syndrome is also low (1–3/million population/year), with a female preponderance, pituitary mediated ACTH production being responsible for up to 80% of these cases.
Aim
To present the difficulties in the differential diagnosis of ACTH dependent hypercortisolism in a patient with previous medullary thyroid carcinoma.

Patient and methods
A 53 year old woman with thyroidectomy for MTC in 2009 (preoperative calcitonin levels >2000 pg/ml; negative CEA), without biochemical or imagistic evidence of recurrence 9 years after, presented in our department for significant weight gain, peripheral edema and high blood pressure (SBP~190 mmHg).
Methods
TSH, FT4 and calcitonin were measured by chemiluminescence. Serum cortisol and plasma ACTH were measured by electrochemiluminescence. We also performed: 1-mg overnight dexamethasone suppression test (1-mg DST) and 48-h, 2mg/d low-dose DST (LDDST) ; immunohistochemistry of thyroid tumor for calcitonin, CEA, SSTR2, SSTR5, TTF1, Ki67 and ACTH; pituitary and adrenal imaging by MRI, cervical and thoracic imaging by CT scan.
Case report
Clinical examination showed gynoid obesity (BMI=41.95 kg/m^2), BP=175/100 mmHg, normal visual field, but no purple striae or hirsutism; galactorrhea or extremities enlargement were absent. There were no palpable cervical masses. Hormonal assessment revealed increased 8 AM serum cortisol (22.38 μg/dl) and plasmatic ACTH (72.66 pg/ml), loss of nocturnal nadir of serum cortisol at 11 PM (9.76 μg/dl), without adequate suppression of 8 AM serum cortisol either after 1-mg DST (3.93 μg/dl) or LDDST (4.59 μg/dl), normal prolactin and IGF1. ACTH dependent Cushing's syndrome was therefore diagnosed. There was no diabetes or osteoporosis. MRI showed a pituitary adenoma (9.5/5.5/6.5 mm) and bilateral adrenal hyperplasia. IPSS was not technically available, but there wasn't any sign of recurrence of MTC (persistent normal calcitonin and CEA, negative ACTH immunohistochemistry of the thyroid tumor, negative imaging study for local regrowth/distant metastases–ultrasonography, CT scan), neuroendocrine markers were normal (Cromogranin A, 5-HIA, plasmatic metanephrines and normetanephrines) and there were no pulmonary nodules on CT scan. Therefore, Cushing's disease was the most probable diagnosis. Treatment with 2 mg/week of Cabergoline was started. Pituitary surgery is pending.
Conclusion
The reported case is uncommon because previous MTC (with high rates of recurrence/metastases and probability to develop paraneoplastic Cushing's syndrome) was later associated with pituitary ACTH secreting microadenoma. Immunohistochemistry of pituitary adenoma and hormonal postoperative assessment are mandatory for diagnosis confirmation.

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EP353

Diagnosis of panhypopituitarism in adulthood - diagnostic and therapeutic challenges

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Introduction
Combined pituitary hormone deficiency (CPHD) is characterized by impaired production of pituitary hormones. A possible cause are PROP-1 mutations (prophet of Pit-1 protein). It plays an essential role in the evolution of pituitary cells secreting GH, TSH, LH, FSH, prolactin; some patients may develop late ACTH deficiency. PROP 1 gene mutation is manifested with variable degrees of phenotype-genotype correlation, with growth failure as the first sign detected in early childhood. Central hypothyroidism, delayed or absent sexual maturation and ACTH insufficiency occur progressively. On magnetic resonance (MR) imaging, the anterior lobe is usually hypoplastic but may be normal or even enlarged; the posterior lobe and the pituitary stalk are normal.
Case Description
We report a case of a 45 years old romanian man who, was admitted for decreased libido, asthenia. Physical examination–normal stature, overweight (BMI=28.73 kg/m^2, 89 kg), normal blood pressure, without orthostatic hypotension, regression of sexual secondary characteristics, no syndromic abnormalities. No similar diseases in the family history. Serum hormones revealed panhypopituitarism (IGF-1=40 ng/ml, TSH=0.2 mU/ml, fT4=0.60 ng/dl, 8 AM Cortisol=4 mg/dl, FSH=0.24 U/l, LH=0.04 U/l, Testosterone=0.63 ng/ml) and an initial elevated Prolactin (39.2 ng/ml) but after precipitation the prolactin was also low. Pituitary MR imaging showed a normal aspect of the pituitary (LL=14.5/AP=8.7/CC=4 mm), without enhancement after contrast infusions. The stalk and the neurohypophysis appear in normal position. Blood DNA analysis for PROP-1 gene defects are in progress.
Conclusion
The findings illustrates combined pituitary hormone deficiency at adult age–this is quite exceptional, but further investigation is considered - DNA analysis of PROP-1 gene defects. The PROP-1 mutations are currently the most frequently recognized genetic cause of CPHD. Substitutive hormone treatment is introduced to this patient with 75 μg oral Levothyroxine, 10 mg oral Hydrocortizone and Testosterone gel, with a good clinical and biological result.

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EP354

Crooke's cell adenoma and cushing disease: A severe case report

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Introduction
Cushing's disease (CD) is a potentially fatal disease caused by corticotrophic adenoma of the pituitary gland. Crooke Cell Adenomas (CCA) are a rare variant characterized by cytoplasmic ring deposits of cytokeratin filaments. They are usually aggressive macroadenomas with a higher rate of recurrence and malignancy.
Clinical case
A 36 year old man, with 34 kg weight gain and uncontrolled hypertension for 4 years presented at the Emergency Department In September 2018 with new onset dyspnea for small exertion, orthopnea and paroxysmal nocturnal dyspnea, BP 201/152 mmHg, heart rate 135 bpm, normal cardiopulmonary auscultation and hepatomegaly. Laboratory workup: metabolic alkalosis, hypoxemia, normocapnia and hypokalemia, serum creatinine 3.9 mg/dl and a troponin rise from 262 ng/dl to 624 ng/dl (VR <34.2 ng/dl). ECG without changes. Acute heart failure was admitted with an AMI without ST elevation and acute kidney injury. Coronary angiography was postponed. Echocardiogram: concentric ventricular hypertrophy, LVEF 40% with lateral segmental hypokinesis. Fundoscopy: severe hypertensive retinopathy. In the ward, hypertension persisted despite 5 antihypertensive drugs and also refractory hypokalemia. When observed by the Endocrinologist it was noted his central obesity (IMC 36 kg/m2), moon face, thin skin, violaceous striae, and decreased proximal muscular strength. Laboratory tests: baseline cortisol and ACTH, 13.2 mg/dl and 57.7 pg/ml, respectively; Cortisol after DXM low dose–7.2 mg/dl and after high dose–7.2 mg/dl. Pituitary MRI: 7 mm posterior intrasellar lesion with slight lateralization to the right, probably cystic". Inferior petrosus sinus catheterization: basal ACTH central/ peripheral gradient of 33.2 and after CRH stimulation 40. Metyrapone 750mg/day was instituted, with progressive improvement in blood pressure control. Submitted to endoscopic transphenoidal surgery with removal of the pituitary lesion without complications. Serum cortisol 17 h after intervention–0.7 mg/dl. Discharged under hydrocortisone 40 mg, amlodipine 10 mg, carvedilol 25 mg and enoxaparin 40 mg/day, with controlled arterial tension and stable renal dysfunction. Histology: solid large cell tumor with abundant cytoplasm, without atypia. ACTH+on the surface and ring cytokeratin in the cytoplasm; Ki67 <3% - Crooke Cell Adenoma. Over the next 15 months, progressive improvement in blood pressure control and kidney function. Hidrocortisone was stopped on the 13 month, and he remains without biochemical evidence of hypercortisolism
Discussion
This case illustrates the serious consequences of prolonged endogenous hypercortisolism. The posterior location of the pituitary lesion raised doubts about its causal relationship with CD and the best neurosurgical approach. Albeit in remission, a careful follow up is indicated, namely considering the histologic type of the corticotrophic adenoma.

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EP355

Craniopharyngiomas: experience of the endocrinology department EPH bologhine west of algiers

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Craniopharyngioma is a slow growing benign epithelial tumor, growing from the pituitary stalk or pituitary gland in the sellar and/or parasellar region. Despite its benignity, the quality of life of patients is most often altered, due to the endocrine, visual and neuro-intellectual sequelae linked to the tumor itself and/or its treatment, as well as a high rate of recurrence. local. Early diagnosis remains the determining factor in prognosis. The objective of this study is to report the experience of the Endocrinology service of EPH Bologhine through the analysis of 31 records of patients hospitalized for craniopharyngioma.
Materials and methods
This is a retrospective study including 31 patients (15 women and 16 men) including 13 children and 18 adults, average age 23 years.
Results
Neurological manifestations are the predominant mode of disclosure 54.8% (17/31) with a picture of intracranial hypertension (42%). On the endocrine level, the somatotropic deficit is found in 25% of patients, the same portion is noted for the gonadotropic deficit. The corticotropic and thyrotropic deficit each represent 41.9% of cases. Stress delay was found in 6.7% of patients and diabetes insipidus 41.9%. Visual disturbances are found in 74.2% (23/31) of patients with blindness in 16.1% of cases. On the radiological level, the suprasellar localization is found in 32% of the cases, calcifications are found in 13% of the cases. The size of the lesion ranged from 18 mm to 63 mm.
Discussion
Craniopharyngioma is a benign, curable tumor, but due to its intimate relationship with critical structures of the central brain such as the optic structures, the pituitary gland, the hypothalamus, intracranial vascularization, the brainstem and the temporal lobes, its grip in charge introduces the risk of long-term morbidity of treatment. Today, the most common therapeutic approach is conservative subtotal resection followed by radiotherapy, and the goal is to limit long-term toxicity. Many recent advances in the treatment of craniopharyngioma are attributable to improvements in surgical techniques and radiotherapy technologies.
Conclusion
The management of craniopharyngioma requires multidisciplinary cooperation. Surgery remains the main treatment.. Today, the most common therapeutic approach is conservative subtotal resection followed by radiotherapy, and the goal is to limit long-term toxicity. Many recent advances in the treatment of craniopharyngioma are attributable to improvements in surgical techniques and radiotherapy technologies.

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EP356

Panhipopituitarism due to inoperable cavernous sinus meningioma

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Panhypopituitarism refers to decreased production of all of the pituitary hormones of the adenohypophysis with or without deficiency of neurohypophysis function. The development of the disorder is frequently insidious and the manifestations often depend on the etiology of the condition.
Case report
In October 2019 a 57-year-old man collapsed in front of the hospital after being discharged from the cardiology clinic. The day before, he had undergone angiographic control for a bicoronary lesion treated in 2018 with Angioplasty with no evidence of restenosis or new lesions. After spontaneously recovering he described previous dizziness without chest pain or palpitations preceding the syncope. On physical examination presented with pale sweaty skin, absent facial hair, blood pressure 100/60 mmHg, heart rate 52/ min raising to 64/min under atropine. No evidence of hematoma, no changes on the EKG nor on the ultrasound, no arrhythmia or sinus pauses were detected on 24 h Holter. Blood sample showed a mild normochromic normocytic anemia and hyposodemia. Brain CT scan described an expansive intracranial process 36/43 mm axial and 33 mm cranio-caudal, with intense iodophilia, involving the right cavernous sinus with intra- and suprasellar extension, plated to the duramater of the large wing of the right sphenoid, invading the sphenoidal sinus, extending in plaque at the prepontin level and including the right: internal carotid artery, Meckel cavity, the orbit apex and right optic nerve. Re-interrogated, the patient declared having suffered several lipothymia episodes, for which a head MRI was performed on August 2018 describing the exact same lesion. Due to the extensions of the lesion the diagnosis of inoperable right cavernous sinus meningioma was reached. The suspicion of Hypopituitarism is raised for the first time and he is referred for endocrinological exam. Lab results revealed: TSH=3.97 uUI/ml (0.27–4.2), FT4=4.2 pmol/l (10.6–22.7), FSH=1.8 mUI/ml (1.512), LH=0.4 mUI/ml (1.7–8.6 mUI/ml), Testosteron=2.50 ng/dl, 8 AM Plasma cortisol=247.9 nmol/l (171–536 nmol/l), ACTH=33.29 pg/ml, Prolactina=555 uUI/ml (98–456), GH <0.05 ng/ml, IGF 1=68.6 ng/ml (81–225). Substitution treatment with prednisone and levothyroxine was initiated, with testosterone substitution being further considered.
Conclusions
Diagnosis and treatment of hypophysis insufficiency can sometimes be delayed. This case emphasises the importance of a thorough anamnesis and data integration in the investigation process. Screening of hypopituitarism in a defined risk populations may prevent under-diagnosis and reduce the severity, extent and duration of the condition.

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EP357

Pituitary apoplexy

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Introduction
Pituitary apoplexy is a rare and potentially life-threatening endocrine and neurosurgical emergency, most often linked to hemorrhage or necrosis of a pituitary adenoma.
Observation
We report the case of a 45 year old patient, with a history of chronic headache, hospitalized in the emergency setting for the management of meningeal syndrome with severe headache associated with vomiting, a significant drop in visual acuity, exophthalmos and ptosis of the left eye. Patient treated with antibiotic therapy, benefited from a normal income brain scan. Faced with the finding of a typical dysmorphic syndrome of acromegaly, it is directed to the endocrinology department where the diagnosis of acromegaly is confirmed biologically, the pituitary imaging revealed a necrotic pituitary adenoma.
Discussion
Pituitary apoplexy is defined by the occurrence of a massive necrotico-hemorrhagic reorganization within a pituitary adenoma, the clinical presentation of which varies according to the extent of the hemorrhage, necrosis and edema. It associates brutal headaches, disturbances of consciousness, sometimes severe visual disturbances (this is the case of the patient), and signs of meningeal irritation with in two thirds of cases signs of endocrine deficits often corticotropic. Its prevalence is 6.2 cases/100.00 inhabitants.
Diagnosis of pituitary apoplexy should be considered in all patients with acute severe headache with or without neuro-ophthalmic signs. The initial hormonal and ophthalmological assessment is essential to allow appropriate management. Magnetic resonance imaging (MRI) is the imaging test of choice to confirm diagnosis. Surgery is indicated in the event of severe visual disturbances. The evolution is generally favorable to often depends on a transient pituitary deficit.
Conclusion
Pituitary apoplexy is a rare complication of pituitary adenomas, it must be suspected in the presence of sudden headache with ophthalmological disorders. Its management must be multidisciplinary.

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EP358

Unexpected diagnosis of ACTH dependent cushing syndrome in an old patient with hypertension, osteoporosis and newly diagnosed diabetes mellitus

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Introduction
Cushing syndrome could be missed initially, especially when the presenting features are common in the general population. Before proceeding to the hormonal tests we have to consider that recent studies have shown that up to 50% of patients with CD have different degrees of altered glucose metabolism, up to 80% of CS patients have hypertension independently of their age and sex and hypercorticism changes bone structure and causes vertebral fractures in approximately 70% percent of patients.
Aim
To present a patient with ACTH dependent Cushing syndrome with many complications of Cushing disease but no specific clinical signs.
Patient and methods
A 68 year old obese woman (BMI = 30.4 kg/m^2), known with hypertension, osteoporosis, multinodular goiter presented in 2019 for endocrine assessment and was diagnosed with diabetes mellitus and ACTH dependent Cushing syndrome.
Case report
Physical examination showed central obesity, without facial plethora, without easy bruising, without reddish purple striae, with minimal hirsutism on the upper lip, BP = 140/85 mm Hg despite treatment with 4 antihypertensive drugs. Visual field was normal. Thyroid examination detected a dominant nodule in a multinodular gland, about 4 cm in size (TIRADS 4, BETHESDA 2). Diabetes mellitus was diagnosed and there was no improvement in bone mineral density (BMD) after 2 years of antiresorbtive therapy (Lumbar BMD 2018–0.791 g/cm^2, lumbar BMD 2019–0.767 g/cm^2). Laboratory tests revealed increased basal serum 0800 h cortisol (28.62 µg/dl) and plasmatic ACTH (137.3 pg/ml), increased serum 2300 h cortisol (13.56 µg/dl), unsuppressed 8 A.M serum cortisol after 1 mg dexamethasone overnight test (27 µg/dl) and after two-day, low-dose dexamethasone suppression test (6 mg/dl).The tests suggested ACTH dependent Cushing syndrome. CT scan showed a pituitary macroadenoma and unilateral adrenal hyperplasia. NET markers (5 HIA, serotonin) were normal, apart Cromogranin A which was mild elevated but the patient was taking proton pump inhibitors. Metanephrines and normetanephrines were normal. There were no pulmonary nodules on chest X-Ray scan. Therefore, Cushing disease was suspected. Pituitary surgery is pending.
Conclusion
Simultaneous development and increasing severity of Cushing Syndrome complications such as diabetes, osteoporosis, hypertension in older patient, it's a clinical clue that should trigger the screening, despite the fact that this disease is often diagnosed at younger ages (25 to 45 years).

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EP359

Ex juvantibus diagnosis of undifferentiated diffuse connective tissue disease

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The term "undifferentiated connective tissue disease" (UCTD) represents a stage of disease where clinical symptoms and serological abnormalities suggest autoimmune disease, but they are not sufficient to fulfill the diagnostic criteria of any well-established connective tissue disease (CTD). A 73-year-old man was referred to the 3rd hospital of Tashkent Medical Academy with signs of kidney lesion and the history of treatment at two other medical settings.

Complaints on admission
Exertional dyspnea, productive cough, high temperature (38° C) with chill and perspiration, palpitation, dryness in the mouth with no saliva, pain in joints, including the maxillary ones, nausea and vomiting, anorexia, 10 kg weight loss for 3 months, and expressed general asthenia.

Indicator	Before treatment	day 10	day 24
Blood:			
Hb	87.0	101	109
RBC	3.0	3.1	3.3
Color index	0.8	0.86	0.9
WBC	10	6.3	8.9
Platelets	3.l	3.5	3.55
Stab neutrophils	4%	-	3
Segmented neutrophils	78%	72	74
Eosinophil%	3	4	4
Lymphocytes%	15	16	18
Basophiles%	0	0	0
Monocytes%	4	8	5
ESR mm/h	35	22	18
Blood coagulation time	H–3.4	K–4.10	H-3.6
ALT U/l	20	23	
Total bilirubin µmol/l	13.5	10.8	
Conjugated bilirubin µmol/l	–	–	
Unconjugated bilirubin µmol/l	13.5	10.8	
Glucose mmol/l mmol/l	4.0	5.1	
Urea	16.9	13.6	10.3
Creatinine µmol/l	427.2	214.9	188.3
Total protein g/l	65.0	69.5	68.8
Potassium mmol/l	4.2	4.0	
Haematocrit	29	32	
Fibrinogen/ antithrombin g/l	6.3	4.1	3.9
Prothrombin ratio/index%	105	90	93
MHO	1.2	1.0	1.1

Examination of the patient 2 weeks later: the general condition is satisfactory, slight general weakness; sometimes coughing with light sputum, 2 kg weight gain. Further recommendations for 1 month: prednisolone (8 tab./day), vitamin E (1 caps. by 200 mg twice a day), clopidogrel 75 mg/day. in the evening after meals, calcium D3 (1 tab. twice aday), omeprazole 20 mg/day. Conclusion: This clinical case is of interest in terms of late diagnosis of undifferentiated diffuse connective tissue disease, that, most likely, was difficult to make due to underestimation of multi-organ manifestations of the disease, including the Sjogren's syndrome which is characteristic for collagenosis, as well as due to refusal of the patient from biopsy. The pulse therapy under the umbrella of the antibiotic have rendered a pronounced positive effect and confirmed the main diagnosis on the basis of the effect of treatment (diagnosis ex juvantibus).

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Carcinoid crisis after peptide receptor radionuclide therapy in patient with midgut neuroendocrine tumor.

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Background
Carcinoid crisis (CC) may rarely occur as a complication of general anesthesia/surgery or peptide receptor radionuclide therapy (PRRT) in patients with neuroendocrine tumor (NET). The incidence of CC as a complication of PRRT is underestimated and comes to 10% of all radioisotope therapies. Progressive organ dysfunction, decrease or increase in blood pressure SBP <80 mmHg or >180 mmHg, unexplained tachyarrhythmia with heart rate >120/ min, bronchoconstriction and facial flushing are criteria for CC.
Clinical case
We present a 75-year-old patient who developed a life-threatening cc on the second day after prrt. he had a midgut neuroendocrine tumor (synaptophysin (+), chromogranin (neuroendocrine tumor (synaptophysin), ki67 5%), with metastates to liver, bones, abdominal nodules and right orbit. a long-acting somatostatin analog (saa)–octreotide was administered. the ct follow-up after 8 months showed progression. the patient was qualified for radioisotope therapy with 177 lu-dota-tate. the patient received the first activity of 200 mci177lu-dota-tate without significant complications. after three months, a second activity of 200 mci 177 lu-dota-tate was given. at admission, the patient was in a good general condition. In additional testsslightly increased CRP–12.5 mg/dl, creatinine-1.4–1.5 mg/dl were found. Urine culture was ordered, and Amoxicillin\Clavulanic were administered. On the next day, intravenous 1000 ml 10% Nephrotec was given for kidney protection, followed by 200 mCi 177Lu-DOTA-TATE. 24 hours after administration of PRRT, the general condition worsened. A syncope, atrial flutter with a rapid ventricular rate of up to 200/min, a tendency to hypotension with a systolic pressure of up to 90 mmHg occured and inflammatory parameters increased (CRP-37 mg/dl, procalcitonin 20 ng/ml). The patient was significantly weakened, with edema, short breath, oliguria, abdominal pain, without diarrhea. Facial flushing dominated. The ciprofloxacin and ceftriaxone, fluids, diuretics, metoprolol and amiodarone were administered. Due to persistent facial flushing and mentioned above signs, CC was diagnosed. Intravenously bolus of 200 μg octreotide, then 100 μg every 6h were given. Daily urine collection showed significantly increased excretion of 5-HIAA-69 mg/24 h (N:2–9 mg/24 h) before and 76 mg/24 h after octreotide injection. No bacterial growth was found in the blood and urea. Treatment with short-acting somatostatin analogues was continued. On the fifth day after PRRT administration, the sinus rhythm returned and the patient's condition improved.
Conclucion
Potential causes of carcinoid crisis in this case might be: injection of last SAA dose 3 months before PRRT, tumor lysis syndrome after PRRT, overproduction of serotonin from lysine and arginine given as nephroprotection or partially all of them.
The next PRRT, should be proceeded with use of short-acting somatostatin analog immediately after PRRT as the protection against the CC.

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EP361

The management of acromegaly: experience of the endocrinology–diabetology department of oujda's mohammed vi university hospital, morocco

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Introduction
Acromegaly is a rare disease characterized by somatotropic hypersecretion. The disease is associated with multiple significant comorbidities and increased mortality. The purpose of this study is to describe the epidemiological, clinical, para-clinical and therapeutic features of Acromegaly disease.
Patients and methods
This is a retrospective study including 12 patients with acromegaly in the Endocrinology Diabetology Department of Oujda's Mohammed VI University Hospital, MOROCCO.
Results
The mean age at diagnosis was 55 years with a female predominance. The median diagnosis delay was 8 years. Acrofacial dysmorphic syndrome was the most frequent mode of revelation. Pituitary adenoma was the etiology in all cases: macroadenoma in 11 patients and microadenoma in one patient. All our patients had complications at the moment of diagnosis: ante-pituitary insufficiency in 100% of cases, ophthalmological disorders in 75%, cardio-respiratory complications in 60%, diabetes mellitus was found in 58% and dyslipidemia in 25% of cases. All our patients had goiter. Colic polyps were observed in 41.6%, bone deformities in 50% and arthralgia in 50%. 75% of patients underwent transsphenoidal pituitary surgery. Surgery reduced the level of IGF1 by 41% and the size of the pituitary adenoma by 33%. 83.3% have been treated by somatostatin analogs SSAs (Lanreotide LP 120 mg), given before surgery in 4 cases with non-invasive adenoma and in 5 cases as a second line therapy after incomplete tumor resection associated to radiotherapy (25%). Treatment with SSAs has allowed IGF1 to be normalized in 62.5% of cases.
Conclusion
Acromegaly is a serious condition, associated with multiple comorbidities and increased mortality. Early identification of the signs and symptoms of the disease by health care professionals knowledgeable about acromegaly may help to mitigate this delay. Treatment can then be initiated promptly, with the potential to reduce mortality. Its management should be discussed among multidisciplinary meetings.

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EP362

Management and outcomes of prolactinoma: follow-up of 40 patients

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Introduction
Prolactinomas are the most common pituitary adenomas. Dopamine agonists (DAs) are the treatment of choice for prolactinomas. Patients with prolactinomas normally are treated in ambulatory. In some patients there are challenges in therapy, and they need to be hospitalized.
Objective
To study the clinical features and outcomes of in-patients with prolactinoma.
Materials and methods
A retrospective analysis of 40 hospitalized Patients with prolactinomas was done. MRI-findings, type and the effect of therapy have been analyzed.
Results
Forty patients (18 (45%) men, 22 (55%) women) were included into the study. Eight patients (20%) had microprolactinomas and 32 (80%) harbored macroprolactinomas. The main reasons for hospitalization were: 30 (75%) patients were referred from different regions of Russian Federation due to ineffectiveness of routine treatment, 8 (20%) were transferred from the neurosurgery department after adenomectomy and 2 (5%) were hospitalized due to the suspicion on MEN1 syndrome. 11/40 (40%) patients used cabergoline in dose less than 2 mg/week with prolactin levels normalization and adenoma volume reduction. This group of patients can be considered as sensitive to DAs. Due to an allergic reaction, cabergoline therapy was discontinued in one patient; after that was performed adenomectomy followed by normalization of prolactin levels. 2/40 patients were initially treated with bromocriptine (7.5–12.5 mg/day) and led to the normalization of prolactin and a decrease in adenoma volume. 16/40 (40%) patients used cabergoline in dose more than 2 mg/week without prolactin levels normalization. This group of patients can be considered as resistant to DAs. In 8/16 (50%) patients doses were increased (to 3.5–4.5 mg/week), in 4 patients it led to normalization of prolactin levels. In 2/16 (12.5%) patients cabergoline was changed to bromocriptine (7.5–10 mg/day), in 1 patient it led to normalization of prolactin levels. Adenomectomy was performed in 6/16 (38%) patients; however, surgery did not lead to normalization of prolactin in 3 cases. 10/40 patients (25%) underwent adenomectomy without achieving the maximum tolerated doses of DAs, only 3 of them had emergency indications for surgery.
Conclusions
The use of high doses of DAs can lead to normalization of prolactin levels, as well as a reduction of more than 30% of the tumor volume with long-term treatment. The increasing of doses of DAs to the maximum tolerated, using a combination of non-selective and selective DAs can lead to prolactin levels normalization and reduce the number of surgical interventions among patients with prolactinomas.
Keywords: bromocriptine, cabergoline, prolactinoma, resistance.
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EP363

Metastatic neuroendocrine tumor of unknown primary site with associated carcinoid syndrome in a young patient–a case report

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Background
Neuroendocrine tumors (NETs) are relatively uncommon, accounting for 10 to 14 percent of all neuroendocrine neoplasms. Twelve percent to 22% of patiens are metastatic at presentation. The most frequent primary sites are the gastrointestinal tract (62–67%) and the lung (22–27%).
Case presentation
We report the case of a 36-year-old female patient diagnosed with metastatic disease, with liver, lung and lymph nodes metastasis with unknown primary tumor site, diagnosed on magnetic resonance imaging (MRI) at the age of 34. At her first evaluation in our clinic, she presented both clinical and paraclinical signs of carcinoid syndrome, with hot flashes, increase in stool frequency and with increased neuroendocrine markers (Chromogranin A = 100 ng/ml, Serum Serotonin = 1187 ng/ml, Neural Specific Enolase = 11.6 ng/ml). Further imaging studies showed progression of the metastatic disease, with the increase both in size and number of the liver metastasis (the largest from 9 cm in December 2017 to 14 cm in August 2019) and a lung tumor increasing in size, from 1.71 cm to 8.57 cm withing the last year. She was put on somatostatin (SS) analogues (Octreotide) with increasing doses, up to 60 mg every 28 days. We mention a twin pregnancy lost at 17 weeks in July 2019, on the course of which the patient stopped treatment with Octreotide. In December 2019 she received 7.4 GBq177-Lu-DOTATOC withing the first session of peptide receptor radionuclide therapy (PRRT), with the arousing of suspicion that the primary tumoral site might be the lung lesion, as seen of PET-CT.
Conclusion
We presented the case of a 36-year-old patient with a neuroendocrine tumor of unknown site, with rapidly progressing metastatic disease, with poor response to SS analogues, with a very poor prognosis for tumor-free survival.

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EP364

Insulinoma localized by Ca-stimulation angiography: A case report

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Introduction
Insulinoma is a rare tumor of the beta cells of the pancreas. The clinical manifestation is diverse with hypoglycemia and autonomic neurological symptoms. For diagnosis the Whipple's triad needs to be present: signs of hypoglycemia, glucose level under 3 mmol/l and the cessation of symptoms after administration of iv. glucose. The fasting test confirms the diagnosis. The most commonly used imaging techniques that may localize the tumor are the abdominal ultrasound and CT scan; however, in some cases further procedures are necessary.
Case report
A 27 years old male patient without any other significant disease in his history presented with symptoms lasting for one year involving dizziness, fatigue, confusion, sweating and tremor. Blood glucose under 2 mmol/l was found on multiple occasions while presenting specific symptoms, which ceased every time after administration of iv. glucose. During the fasting test a low glucose level with consecutively elevated insulin and C-peptide levels were measured. In order to localize the tumor different imaging techniques were performed. Abdominal sonography, endoscopic ultrasound and spiral CT couldn't find the suspected pancreatic tumor. Finally selective arterial angiography was performed with Ca-stimulation. After selective catheterization of the arteria lienalis, mesenterica superior and gastroduodenalis Ca-stimulation was performed. After administration of iv. calcium blood samples were collected from the right hepatic vein after 0.30 and 60 seconds. During the stimulation administered in the a. lienalis the 1-minute sample showed a significant rise in the insulin and C-peptide levels while after performing the stimulation on the other two arteries no remarkable differences were noticed. The concomitant arteriography showed a small, 1 cm diameter hyper vascularized nodule, characteristic for insulinoma.
Discussion
After establishing the diagnosis, the precise localization of the tumor within the pancreas can become a serious problem. According to the literature 10–27% of the insulinomas cannot be evidenced by the available imaging techniques. The selective Ca-stimulation technique can shrink the possible tumor localization to the region of the pancreas that is supplied with blood by the specific catheterized artery. With this procedure the majority of the pancreas can be saved. Although newer techniques, like GLP1 scintigraphy or sensitive intraoperative ultrasound became available recently, the selective Ca-stimulation can still be used for the identification of insulinomas non-detectable by less expensive noninvasive methods.

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EP365

Acromegaly in young patients - treatment challenges, case presentation

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Introduction
Acromegaly is a debilitating, indolent disease that develops over several years due to extended exposure to elevated growth hormone (GH) levels. It is most commonly caused by somatotropinomas. It represents a rare pathology with an incidence of 3–14 cases per 1 million inhabitants and a prevalence of 40 to 90 cases per 1 million inhabitants. Pituitary adenomas respresent a challenging disease in young patients. Transphenoidal surgery is the best therapeutic option, but in many cases complete biochemical control is difficult to obtain, often requiring adjuvant therapy.
Materials and methods
We present the case of a male patient, 22 years old, diagnosed in 2014 with somatotropinoma. Clinically, on admission, the patient presented drug resistant headache, decreased visual acuity, extremities enlargement and arthralgia. Biological, the patient had elevated IGF–11 (726.9 ng/ml) and basal GH (116 ng/ml) levels and gonadal insufficiency. The MRI evaluation revealed the presence of an invasive macroadenoma (32/36/26 mm), with the inclusion of the optic chiasm and severe bitemporal hemianopsy. The recommendation at diagnosis was transphenoidal adenomectomy, performed in the same year. Postoperatively, the patient presented multiple postoperative complications with the development of global pituitary insufficiency. Postoperative biochemical profile improved, but with GH secretion (10.2 ng/ml) persistence and elevated IGF-1 concentrations (712.6 ng/ml). Treatment with somatostatin analogs and dopamine agonists was initiated after surgery, but GH secretion pursued (6.73 ng/ml). GH receptor antagonist therapy was added to the initial regimen, normalizing IGF-1 concentration (388.00 ng/ml), but with persistent GH secretion (7.78 ng/ml). Radiation therapy with conventional fractionated photons or radiosurgery with proton beam is recommended in this case.
Results
The patient presented a GH secreting pituitary macroadenoma with multiple acute postoperative complications, not responsive to drug therapy. The patient developed multiple complications of acromegaly, impairing quality of life and darkening long term prognosis.
Conclusions
Treatment of acromegaly is challanging in pituitary macroadenomas, especially in young patients. Early diagnosis with therapeutic interventions can improve disease complications, improving quality of life.

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EP366

Recurrent cushing's disease and pregnancy: A case report

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Introduction
Cushing's disease (CD) is reported in 60-70% of all patients with Cushing's syndrome (CS), but occurs only in approximately 33% of the reported CS cases in pregnancy. Nevertheless, despite its rarity, pregnancy in patients with CS can be troublesome because of the risk of maternal-fetal complications.

Observation
A 28-year-old female patient was referred to our endocrinology department for a suspected CS with morphological alterations and recent diagnosed diabetes mellitus. The clinical, laboratory, and imaging findings were compatible with CD and a secondary hypogonadotropic hypogonadism due to pituitary macroadenoma of 17 mm. The patient underwent transsphenoidal resection of the adenoma. No complications arose during the operative and postoperative period. The anatomopathological study disclosed a corticotroph-cell adenoma. Postoperatively, the patient had normal adrenalism. Five and seventeen months after the surgery, respectively, she had two pregnancies with successful maternal-fetal outcomes. The patient remained in remission with no clinical symptoms of CS. Biochemical workup after 5 years and 10 months was as follows: 24 h UFC 150 µg; ACTH 156 pg/ml and serum cortisol measured at 0800 h. after 1 mg dexamethasone administration at midnight 20 ng/ml. Pituitary MRI revealed an adenoma remnant invading the cavernous sinus. Thus, recurrent CD was confirmed. Just a month later, the patient got pregnant. She is now in her first trimester. After a thorough discussion of the risks and benefits to both her and the baby, she elected to proceed with no medical nor surgical treatment.
Conclusion
Pregnancy in women with a diagnosis of CD is an extremely rare event and its diagnosis and treatment are a real medical challenge. The impact of achieving biochemical remission on fetal outcomes is unknown.

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EP367

Diagnosis of multiple endocrine neoplasia type 1 in a patient with hypercalcemia and hyperprolactinemia

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Multiple endocrine neoplasia type 1 is a rare autosomal-dominant disorder. The most common endocrine tumors are parathyroid tumors, which cause hyperparathyroidism and hypercalcemia. Other tumors of MEN 1 include pituitary tumors for example prolactinomas and enteropancreatic tumors such as gastrinomas, insulinomas, VIPomas, carcinoid tumors. We report a case of a 31 year old male with MEN 1 presenting hypercalcemia with complaints of fatigue and weakness. On further questioning, the patient reported to headache and decreased libido. Laboratory results revealed: serum calcium: 11.27 mg/dl (8.6–110), intact parathormone: 101.1 pg/ml (15–165) phosphor: 2.64 mg/dl (2.6–14.5), prolactin: 1597 ng/ml (4.04–115.2), gastrin 17 pg/ml (13–1115), insulin: 19.79 uU/ml. A cranial MRI revealed 3 cm diameter cystic macroadenoma on the center of pituitary gland. The upper abdominal MRI was scanned for exploratory purpose and did not revealed any tumors. Hyperparathyroidism and pituitary macroadenoma were accepted as MEN 1 components. The patient underwent the operation for resectomy of the pituitary mass. Parathyroidectomy and profilactic thymectomy operations were planned. Although hypercalcemia with hyperprolactinemia is a a rare condition, it should be kept in mind that finding of hyperparathyroidism and hyperprolactinemia togetherness may be the signs of the Men 1 syndrome.

Keywords: MEN 1, hyperparathyroidism, pituitary tumors, pancreatic tumors.

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EP368

ACTH-dependent cushing's syndrome: an overview of the clinical features, diagnosis and treatment in the endocrinology-diabetology and nutrition department of oujda's mohammed vi university hospital - morocco

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Introduction
Cushing's syndrome is a rare condition, resulting from chronic exposure to excessive circulating levels of glucocorticoids. This condition is highly associated with complications such as cardiovascular and metabolic disorders. This study aims to review the clinical characteristics, diagnosis and treatment of patients with ACTH-dependent Cushing's syndrome.
Material and methods
A descriptive and comparative study carried out in the Endocrinology-Diabetology-Nutrition department of Oujda's Mohammed VI University Hospital, Morocco. The population study included 15 patients with ACTH-dependent Cushing's syndrome.
Results
The mean age of the patients was 31.7 years (extreme ages 14–151 years) with a female predominance. All patients showed symptoms of hypercortisolism. All patients had elevated midnight blood cortisol, loss of cortisol circadian rhythm and non-suppression of cortisol during 1mg overnight dexamethasone suppression test. All patients responded to 8mg dexamethasone suppression test. The mean ACTH value at the moment of diagnosis was 141.9 ng/l. The hypothalamic-pituitary MRI revealed a pituitary microadenoma in 46.7% of the cases, a macroadenoma in 20% and was negative for 33.3% patients. 7 patients out of 15 received preoperative medical therapies: 42% were treated with Metopirone, and 58% were treated with Ketoconazole. 42.8% of the patients have undergone transsphenoidal surgery for their pituitary adenoma, while 50% had a bilateral adrenalectomy. Fifteen percent of patients needed post-operative conventional radiotherapy and one patient underwent radiosurgery. Meanwhile, one patient refused treatment. The remission rate was around 33.3%. However, 50% experienced an adenoma recurrence.
Conclusion
Cushing's disease is caused by a pituitary ACTH-secreting adenoma, causing endogenous hypercortisolism. The management of Cushing's disease and its complications should be discussed over multidisciplinary meetings, including endocrinologists, neurosurgeons and radiologists in order to choose the best treatment plan for the patient.

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EP369

Family case of multiple endocrine neoplasia type 1 in belarusian population

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Introduction
Multiple endocrine neoplasia type 1 (MEN-1) is a rare, autosomal dominant inherited disorder, characterized by a high predisposition to develop a wide spectrum of endocrine and nonendocrine tumors, mostly of parathyroids, endocrine pancreas, and anterior pituitary.
Methods
Analysis of clinical and laboratory data, family history of multiple endocrine neoplasia.
Results
A 19-year-old woman with autoimmune thyroiditis and hypothyroidism was routinely examined in outpatient Endocrine Department in Minsk (Belarus). Replacement therapy with levothyroxine 50 mg was prescribed 2 yrs ago. She complained sickness, in the anamnesis–eating behavior disorders with body mass fluctuations during last year. Occasionally low levels of serum potassium were revealed and she was hospitalized in Medical Academy Clinic. It appeared that her mother had pituitary macroadenoma (somatotropinoma) and primary hyperparathyroidism with hypercalcemia, verified in 2019 yr. She was prescribed aledronic acid medication to control the levels of serum calcium. Parathyroid surgery was postponed because of unclear reason. Mother's sibling and nephews are living in Germany and MEN-1 mutation was verified in their family. Their MEN-1 phenotype was characterized by primary hyperparathyroidism, pituitary adenoma. Pancreas tumor was diagnosed in one family member 48 years old. New anamnesis data influenced the diagnostic protocol in our patient - increased levels of PTH were diagnosed (255.0 ng/l, reference range, 10–65 ng/l). Routine biochemistry revealed near normal Calcium level of 1.35 mmol/l (reference range, 1.12–1.32 mmol/l). She had no symptoms of hypercalcemia. Parathyroid scintigraphy was normal. Serum potassium levels became near normal

on infusion therapy (3.9 mmol/l). Screening for parathyroid, pancreas endocrine tumors and pituitary adenoma started.
Conclusion
Primary hyperparathyroidism is the most frequent and usually the earliest expression of MEN-1, with typical age of onset at 20–25 years. Early detection of the disease and correct treatment are therefore of great importance. Education of members of families with MEN-1 is worth doing as well as molecular screening for MEN-1 mutation to individualized their diagnostic and treatment protocols.

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EP370

Latrogenic cushing syndrome owing to topical steroids

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Topical steroids are widely used by dermatologists and other physicians for the treatment of skin diseases such as diaper dermatitis. Iatrogenic Cushing syndrome may occur as an undesirable outcome of high-dose glucocorticoids treatments. This may also cause hypothalamus–hypophysis– adrenal axis suppression. While this situation may be caused more frequently with oral and topical glucocorticoid therapy, iatrogenic. Here, we report a 6 month-old boy with Cushing syndrome that was developed secondary to potent topical corticosteroid (diflucortolon valerate) use 3 to 4 times daily for 4 months. We tried to warn the physicians about the warning signs of Cushing syndrome in patients who suffer from regional obesity, and emphasized the importance of explanation of the usage, and duration of treatment while prescribing topical steroid creams especially during infancy.

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EP371

ACTH-secreting pituitary macroadenomas about tow cases

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Introduction
Cushing's disease is a rare condition observed in about 8–10% of patients with pituitary tumor. In the majority of cases, corticotroph adenomas are small, intrasellar and less than 10mm in diameter, while macroadenomas occur in 4–10% of the patients. An observation of two clinical cases is reported.
The observation
Case number 1: a female patient aged 31, hospitalized for suspected Cushing's disease. Diagnosis mentioned in the context of an exploration for fracture osteoporosis. The 24-h urinary free cortisol (UFC): 560 nmol/l, ACTH: 148.9 pg/ml, midnight cortisol: 350 nmol/l. With pituitary MRI: pituitary macroadenoma of 19 × 10 × 13 mm, extending to the level of the right cavernous sinus, arriving in contact with the right internal carotid artery without invading it. High-dose dexamethasone overnight suppression test, and a corticotrophin releasing hormone (CRH) test, were positive. The patient had a trans-sphenoidal adenomectomy with histological confirmation, corticotropic adenoma KI67 at 7%. The post-operative evaluation at 3 months is in progress. Case number 2: 60 year old male patient with a history of hypertension, type 2 diabetes, sleep apnea syndrome. Diagnosis is supected in front of the clinical aspect suggestive of a cushing syndrome. The 24-h urinary free cortisol (UFC): 5760 nmol/24 h, ACTH: 183.3 pg/ml. Pituitary MRI: macro adenoma of the anterior pituitary gland measured at 14 × 15 × 15 mm, developed mainly on the right side without invasion of the pituitary stem without invasion of the optic chiasm or carotid arteries. High-dose dexamethasone overnight suppression test was negative, but corticotrophin releasing hormone (CRH) test was positive. Patient referred in neurosurgery.
Conclusion
Cushing's disease is rare, even rarer in corticotropic macro adenomas, the latter can be secreting and clinically symptomatic, are often associated with less glucocorticoid suppression than micro adenomas, and pose a problem of management since they are often severe and aggressive.

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EP372

Pasireotide therapy in a patient with pituitary macroadenoma and asymptomatic acromegaly resistant to first generation somatostatin analogues

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Introduction
Acromegaly increases morbidity and mortality and should be treated even in the asymptomatic phase. It is almost always caused by a GH-producing pituitary adenoma and although transsphenoidal surgery is the treatment of choice in most cases, in others, primary medical therapy is indicated.
Clinical case
A 36-year-old female with a family history of thyroid functional pathology and diagnosed with micronodular goiter was evaluated in February 2015 for a transient minimal galactorrhea, unrelated with drugs and without other associated symptoms or signs. In the biochemical tests the following was observed: IGF-I 640 ng/ml (100–330), GH 1.4 ng/ml (0–4.3). Prolactin, FSH, LH, estradiol, cortisol, T4-free and TSH, calcium, phosphorus, renal and hepatic functions were normal. Pituitary magnetic resonance (MR) detected an increase in pituitary size at the expense of a 20 × 12 × 15 mm-sized lesion, bilaterally predominantly left, minimally hyperintense in T2, with some microcyst, hypointense in T1 and hypocaptant with respect to the rest of the gland. It partially invaded the left cavernous sinus and slightly bulged the upper contour of the gland without compromising the suprasellar structures. The pituitary stalk was discreetly horizontal and somewhat lateralized to the right. Given the existence of a macroadenoma that did not compress the optic chiasma and impossible to eliminate completely due to the extension to the cavernous sinus, Sandostatin LAR IM was prescribed, initially 20 and then 30 mg/month. One year later, the patient remained asymptomatic but, given the absence of a biochemical (IGF-I 674 ng/ml, GH 3 ng/ml) and morphological response we agreed to suspend this therapy and reassess the results of IGF-I with another methodology and performing oral glucose overload (baseline GH 5.2 ng/ml, nadir 2 ng/ml). After confirming acromegaly, in July 2017, we started treatment with Pasireotide-LAR IM 40 mg/month and 3 months later the IGF-I was within normal range. The October 2018 pituitary MR showed a reduction in size of the adenoma to 12 × 9 × 8 mm and that it contacted the left internal carotid artery without extending to the walls of the cavernous sinus. To date, with this therapy, the patient maintains biochemical normality with no significant side effects.
Discussion
In this patient with pituitary macroadenoma without surgery indication and null response to first generation somatostatin analogues, it was not possible to personalize the initial medical therapy. Pasireotide-LAR, chosen as second option, produced a biochemical and morphological response.

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EP373

Pituitary macroadenoma (co-secreting GH and Prolactin)

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A 16 years old boy referred to neurosurgery due to sellar and suprasellar mass. He had a history of retro orbital headache in the last three years. he noticed increase in his height, enlargement of hands and feet. He had one year history of progressive decrease in vision mainly in the left. He did not enter puberty.

Physical examinations
BMI 36 kg/m^2 (more than 95 percentile), Tall height 190 (more than 97 percentile), Weight 130 kg (more than 97 percentile).
He had coarse features, with large hand and feet, oily skin. His visual field examination revealed left temporal hemianopia. He is still Pre pubertal.
Laboratory
GH 40 ng/ml, IGF1 1220 ng/ml (107–584).
FT4 10.0 pmol/l, TSH 0.458 miu/ml.
Cortisol 100 nmol/l, Post ACTH stimulation: Cortisol 300 nmol/l.
Testosterone index 7 (33–106), LH<0.1 IU/l, FSH <0.1 IU/l.
Prolactin 888032 miu/l (86–324).
Diagnosis of Pituitary macroadenoma (co-secreting GH and Prolactin) was made.
Patients was treated initially with cabergoline 0.5 mg po once week with dose escalation. Follow up 2 weeks Octreotide 30 mg IM/4W.
His headache improve, as well Visual field improve.
Follow up Prolactin was 30300 miu/l, After three months follow up, he showed marked Improvement in his visual field, and no more headache disappear. The Prolactine level was 6000 miu/l and IGF1 800 ng/ml (107–584).
MRI showed Minimal regression of the mass
After 6 months follow up.
The Visual field was normal, Prolactin 3000 miu/l, IGF1 650 ng/ml (107–584).
He is still on Cabergoline 1.5 mg twice per weeks and Octreotide 40 mg/4 weeks.
Conclusion
Young patient present with sellar and suprasellar mass. The diagnosis was Pituitary macroadenoma (co-secreting GH and Prolactin) was made.

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Reproductive and Developmental Endocrinology

EP374

Androgen modulate the pro-oxidant and antioxidant activity of macro-endothelial cells

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Introduction
Limited data exist on testosterone and oxidative stress induction. The present study was undertaken to evaluate, in vitro, the role of physiological concentrations of androgens (testosterone-DHT) in modulating the pro-oxidant and antioxidant activity of intact endothelial cells.
Materials and methods
EA.hy926 macroendothelial cells were cultured in DMEM phenol red free without FBS for 24 hours. Growth medium was replaced and then testosterone (0.5 nM), and DHT (0.5 nM) alone or in combination with the androgen receptor antagonist flutamide (50nM), were added to the culture media and cells incubated for 2 more hours. Intracellular reactive oxygen species (ROS) content, endothelial nitric oxide synthase (eNOS) activity, nitric oxide (NO) levels, superoxide dismutase (SOD) activity, catalase activity (CAT), and glutathione (GSH) levels were measured.
Results
Testosterone and DHT significantly increased eNOS activity ($P<0.001$ vs CTL) and NO production ($P<0.001$, $P<0.01$ vs CTL accordingly), while they augmented the intracellular ROS content ($P<0.001$ vs CTL) in EA.hy926 endothelial cells. Moreover, they increased the antioxidative system of SOD ($P<0.001$, $P<0.01$ vs CTL accordingly) and significantly decreased catalase activity ($P<0.001$ vs CTL). All the above effects of androgens were abolished by flutamide suggesting that they act through the androgen receptor. Finally, testosterone and DHT had no significant effect on cellular GSH levels and the GSH/GSH+GSSH ratio in EA.hy926 cells.
Conclusion
Our findings indicate a pro-oxidative role of testosterone and DHT in EA.hy926 endothelial cells, suggesting that the androgens upregulate the endothelial oxidoreductase homeostasis to a higher functional level.

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EP375

Correlations between clinical suppositions, type of chromosomal anomaly and age for confirmation of diagnosis. A retrospective study of X monosomy

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We made a retrospective study of X monosomy cases identified in our laboratory in the last 10 years. The aim of study was to establish a correlation between different forms of X monosomy, and age for confirmation of cytogenetic diagnosis. Between 2010 and 2019 we confirmed 81 cases of Turner syndrome in our laboratory. We found different forms of X monosomy and the most frequent was X homogenous X monosomy. We found 24 cases (29.62%) of X homogenous monosomy (median age of diagnosis–7 years) 14 cases (17.28%) of 45, X/46, X, I (Xq) (median age of diagnosis–14 years) 11 cases (13.58%) of with deletions on chromosome X (median age of diagnosis–10.5 years) 9 cases (11.11%) with 45, X/46, XX (median age of diagnosis–25 years) 9 cases (11.11%) with complex forms of chromosomal mosaics that included a line with X monosomy (median age of diagnosis–23 years) 7 cases (8.64%) with ring chromosome X (median age of diagnosis–8.75 years) 3 cases (3.7%) with X monosomy and the presence of a marker chromosome (median age of diagnosis–3.75 years) and 5 cases (6.17%) with other unbalanced structural anomalies of chromosome X (median age of diagnosis–6.25 years). We confirmed the diagnosis at a small age in cases with X homogenous monosomy, ring chromosome X or a marker chromosome. For example, in 10 of 24 cases with X homogenous monosomy the age for confirmation of diagnosis was before 1 year. In opposition, the presence mosaic forms were correlated with a high median age (more than 20 years). The chromosomal analysis in our cohort was imposed by different clinical suppositions: Turner syndrome–58 cases (71.6%) amenorrhea or feminine sterility–8 cases (9.87%) short stature–7 cases (8.64%) plurimalformative syndrome–4 cases (4.93%) loss of pregnancies–2 cases (2.46%) and intersexuality–2 cases (2.46%). A feature or a complete pattern of Turner syndrome was discovered in 73 cases (90.01%) and such situation was identified in all cases with homogenous X monosomy or ischromosome X. Our study confirmed the importance of a good collaboration between geneticists and endocrinologists in management of Turner syndrome. Also, we confirmed the importance of cytogenetic analyses that are mandatory in management of Turner syndrome.

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EP376

Thyroid peroxidase antibodies in women with polycystic ovary syndrome and type 1 diabetes

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Objective
Polycystic ovary syndrome (PCOS) is more prevalent among women with type 1 diabetes (T1DM) than in general population. Autoimmune thyroiditis (AIT) is the most common autoimmunological disease in young women in reproductive age, especially in T1DM. Data in literature indicate the possible role of thyroid autoimmunity in PCOS pathogenesis. It has been suggested that positive concentration of thyroid peroxidase antibodies (TPOAbs) is associated with increased prevalence of PCOS. Data in women with PCOS

and T1DM are not known. The aim of this study was to evaluate the presence of TPOAbs and its relationships with clinical and laboratory parameters in women with PCOS and T1DM.
Patients and methods
We studied 83 women with T1DM (age 26±5 years, BMI 24±3 kg/m^2): 41 with PCOS and 42 without PCOS. PCOS was diagnosed using the Rotterdam criteria. Anthropometric measurements, clinical parameters, ultrasonographic evaluation of the ovaries, assessment of serum concentrations of sex hormones, TPOAbs, TSH, free triiodothyronine and free thyroxine were performed for all women.
Results
In PCOS women, we found 12 women with positive serum concentration of TPOAbs (T1DM+PCOS+TPOAbs) and 29 women with negative serum TPOAbs (T1DM+PCOS+noTPOAbs); in the group without PCOS, 18 had positive serum TPOAbs. The prevalence of positive TPOAbs concentration did not differ between women with and without PCOS. Groups T1DM+PCOS+TPOAbs and T1DM+PCOS+noTPOAbs did not differ in anthropometric measurements, daily dose of insulin, or HbA1c. TSH and free thyroid hormones, as well as hormonal profile were comparable in T1DM+PCOS+TPOAbs and T1DM+PCOS+noTPOAbs. In all PCOS women, TPOAbs concentration correlated significantly with hirsutism score (r=0.48, P=0.001) and ovarian volume (r=0.33, P=0.037).
Conclusions
In T1DM women, PCOS is not related to higher prevalence of positive serum TPOAbs detection.

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EP377

Is there relationship between serum Igf-1 and thyroid nodule, thyroid or ovarian volume in polycystic ovarian syndrome?

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Introduction
Studies investigating the association between serum IGF-1, and thyroid nodule, ovarian or thyroid volume in polycystic ovarian syndrome (PCOS) are limited. We aimed to analyze the association between serum IGF-1 level, and ovarian or thyroid volume, or thyroid nodule in PCOS.
Materials and methods
The study was performed between June 2017 and August 2019 as prospective design. The patients referred to our medical faculty were included. Adult females with new-onset PCOS were included. The patients having comorbid illness, or using medication were excluded. Basic laboratory tests, thyroid and ovarian sonography were performed. The patients were grouped according to thyroid nodule (absent/present) and ovarian volume (<10 ml/≥10 ml). We planned to find a positive association between IGF-1, and thyroid nodule, thyroid or ovarian volume in PCOS.
Results
Of total 118 patients, 11 (9%) had thyroid nodule. The patients with thyroid nodule had a higher thyroid and ovarian volume (P=0.026, P=0.006; respectively). No correlation was found between GH or IGF-1, and thyroid or ovarian volume. IGF-1 was not a predictor for thyroid nodule or higher ovarian volume. The higher DHEAS and thyroid nodule were found as significant predictor for higher ovarian volume.
Conclusions
To our knowledge, our study is the first to analyze the association between IGF-1 and thyroid nodule in PCOS. We found that thyroid nodule was associated with thyroid and ovarian volume, but IGF-1 was not associated with thyroid nodule, thyroid or ovarian volume. It should be kept in mind that metabolic screening is essential but we do not recommend routine measurement of IGF-1 in PCOS.

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EP378

Clinical experience in puerta del mar university hospital anttending transsexual people (2015-2019)

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Introduction
Transsexuality is defined as discordance between one's assigned sex at birth and that individual's gender identity. Hormonal, anatomical, legal and psychosocial adaptations are present in most cases. Following recent changes to the Spanish legal framework, modifications have instaured to the model of attention for transsexual people in Andalusia. The aim of this study was to evaluate healthcare demand evolution in Trans People Attention Unit of Puerta del Mar University Hospital (Cádiz) from April 2015 to December 2019.
Methodology
We conducted a retrospective and longitudinal-descriptive case series study to evaluate healthcare demand evolution in Transsexual People Attention Unit of Puerta del Mar University Hospital (Cádiz) from April 2015 to December 2019. We analyzed demographic characteristics and the percentage of people reciving gender-affirming treatments (hormonal and/or surgery). Rate of loss of clinical follow-up and the psychological support demand are analyzed.
Results
We attended 353 transsexual people: 194 transsexual men and 159 transsexual women. The number of people assessed per year increased from 49 in 2015 to 91 in 2019. The median age at the 1st visit was 19 (17–25) years. 335 people (94.9%) started gender-affirming hormonal treatment (HT). We observed 28.9% mastectomy and 20% hysterectomy plus double anexectomy in transsexual men. 13.7% transsexual women were underwent for feminizing genitoplasty surgery and 15.8% are on surgical waiting list. 18.4% transsexual people (n=64) have required psychological support and 16.5% (n=56) were lost to follow-up.
Conclusions
In our setting, care is provided to a growing number of transsexual people in last years. In most cases, gender-affirming hormonal treatment is performed and psychological support is occasionally demand. No cases of regretted have been detected gonadectomy yet.

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EP379

Semen quality improvement after weight loss by very low-calorie ketogenic dietary: A report of two cases

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Considered as the biggest public health problem, the pandemic growth of obesity is associated to decline of male fertility potential over the last 50 years. Thus far, the effect of weight loss on semen parameters is still controversial and poorly understood. In this study we report the effect of significant weight loss on semen parameters of two obese men with metabolic syndrome. The patients followed to a very low-calorie ketogenic diet (VLCKD) according to a commercial weight loss program (Pronokal® Method), wich includes lifestyle and behavioral modification support. Seminal analysis was performed in according to World Health Organization guidelines, using Maklef counting chamber. Sperm morphology was analized by WHO guidelines and strict criteria (fabric for sperm concentration, motility and morphology). Clinical and hormonal data pre- and *post*-dietary intervention are presented below. Patient 1, weight: 127.8/*101.4* kg, BMI: 42.7/*33.9* kg/m^2, body fat 41.9/*33.9%*, triglycerides 286/*157*, HOMA-IR 11.6/*3.0*; total testosterone 256/*623* ng/dl. Patient 2, weight: 99.5/*90.3* kg, BMI: 31.4/*28.5* kg/m^2, body fat 21.2/*26.3%*, triglycerides 197/*88* mg/dl, HOMA-IR 2.63/*1.29*; total testosterone 388/*351* ng/dl. All semen characteristics expressively improved in both patients. The sperm total and progressive motility increased respectively by 46.4% and 62%% in Patient 1 and by 2.63% and 24.5% in Patient 2. Normal sperm morphology increased from 5% to 8% in patient 1 and from 1% to 5%, in patient 2. In addition, total motile sperm count

increased by 20% and 40% in patients 1 and 2, respectively, after dietary intervention. In conclusion, besides the significant improvement in metabolic and hormonal profiles, our results seem to support the potential benefit of weight loss by VLCKD in improving sperm motility and morphology of obese patients. Further cohort studies involving a larger number of patients should be performed to verify this hypothesis.

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EP380

Effect of significant weight loss by very low calorie ketogenic diet on male obesity secondary hypogonadism and sexual function

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Obesity is the single most significant risk factor for testosterone deficiency in men, with a reported prevalence up of 60% of male obesity secondary hypogonadism (MOSH). Several studies have shown that significant weight loss due to bariatric surgery have significant metabolic and endocrine improvement in obesity, however the results achieved with conventional diet and lifestyle change are poor and not able to reverse this condition. As an alternative to bariatric surgery, we aimed to evaluate the effect of very low-calorie ketogenic dietary (VLCKD) on hypogonadism reversion and sexual function in obese patients. Ten men aged 31–47 years with BMI between 31.7–48.7 kg/m^2 were assigned to the VLCKD intervention following a commercial program of weight loss Pronokal Method. Body weight, visceral fat, HOMA-IR, triglycerides, HDL and testosterone levels were measured at baseline and after two months. International Index of Erectile Function (IIEF–5) questionnaire was used to assess erectile dysfunction at baseline and after six months. Statistical analysis was performed by repeated-measure multivariate ANOVA using STATA 14.2. Results demonstrated mean weight loss of 18.0±3.2 kg (15±2.1%) with a significant improvement in TT levels (150.4±127 ng/dl corresponding to 53±38.9% of the basal; $P=0.005$). IIEF-5 score of six patients was calculated. Four had erectile dysfunction that improved from mild to normal ($n=3$) and from severe to mild/moderate ($n=1$). Furthermore, a significant improvement in metabolic parameters as HDL, triglycerides, HOMA-IR and visceral adiposity were also reported. Compared to data found in meta-analysis (increase of 254 ng/dl/32% of weight reduction), the VLCKD diet seems to increase more significantly baseline testosterone levels. In conclusion, VLCKD significantly increases testosterone levels, improves metabolic parameters and erectile function in men.

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EP381

46, XX male syndrome- testicular disorder of sexual differentiation

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Introduction
46, XX male syndrome–testicular disorder of sexual differentiation (DSD) is a rare condition, that was first described by la Chapelle et al. in 1964. The phenotypes of 46, XX testicular DSD include males with normal phenotype, males with genital ambiguities or males with true hermaphrodites. The diagnosis may be more difficult in adults with normal gender development than in children. Here, we present hormonal and cytogenetic conditions of an adult male who was diagnosed as primary hypogonadism with 46, XX male syndrome.
Case
A 39-year-old male presented with erectile dysfunction, decreased sexual desire and infertility. His height and weight were 163 cm and 75 kg, respectively, with a body mass index of 28.3 kg/m2. On physical examination, he had bilateral painless gynecomastia. His testicles were in the scrotum, but they were small and soft. The size of the penis was small. In laboratory analysis, FSH and LH levels were over the upper normal limit, and total testosterone level was below the normal limit (Table 1). Hormonal analyses showed hypergonadotropic hypogonadism. Scrotal ultrasonography showed small testicles localized in the scrotum (right testicle was 80 × 15 mm, left testicle was 9 × 10 × 17 mm). Spermiogram was performed and it was found to be compatible with azoospermia. Karyotype analysis was performed and 46, XX was detected. FISH analysis and molecular analysis for SRY gene was performed, but the result has not been released yet. After testosterone replacement therapy, the patient's complaints decreased at follow-up.
Conclusion
Hypergonadotropic hypogonadism that develops due to genetic causes is rarely seen. One of them is 46, XX karyotype testicular DSD disorder, which is an uncommon sex reversal syndrome characterized by a female karyotype in discordance with a male phenotype. Diagnosis depend on karyotype, molecular and cytogenetic analysis. Klinefelter's syndrome and mosaic forms should be considered in the differential diagnosis of these rare syndromes, which are differentiated by karyotype analysis. Proper treatment with the timely diagnosis will contribute positively to bone mineral density and their sexual development.

Table 1 Laboratory variables of the patient.

FPG (ng/dl)	82
Creatinin (0.6–1.3 mg/dl)	0.6
ALT (5–50 U/l)	21
AST (5–50 U/l)	26
FSH (1.4-18.1mIU/ml)	31.27
LH (1.5–9.3 mIU/ml)	15.63
Total testosterone (2.49–8.36 ng/ml)	0.569
Estradiol (0–39.8 pg/ml)	16.93
Prolactin (4.04–15.2 ng/ml)	8.75
TSH (0.27–4.1) µIU/ml	1.49

FPG: Fasting plasma glucose, ALT: alanine aminotransferase, AST: aspartate aminotransferase, FSH: Follicle-stimulating hormone, LH: luteinizing hormone, TSH: thyroid-stimulating hormone.

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EP382

TSH levels vis-à-vis total sperm count and testosterone levels

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Introduction
The role of thyroid hormones is important in testicular development and function (involvement in Sertoli cell proliferation and functional maturation control and postnatally in Leydig cell differentiation and steroidogenesis). Additionally, thyroid hormone receptors are found in testicular cells throughout development and in adulthood. Our aim was to study thyroid hormone effects on testicular function.
Materials and methods
We retrospectively analyzed data from a large series of outpatients who were evaluated for couple subfertility in our andrology clinic. Men with thyroid or pituitary disorders, azoospermia or obstructive azoospermia (diagnosed by history, normal FSH levels and, in most subjects, testicular biopsy), previous surgery operation for varicocele, or receiving medications that altered testicualr or thyroid physiology were excluded. A series of 106 unselected men from the records of the clinic were included (mean age±S.D: 34.3±6.1 years, mean BMI±S.D: 27.63±4.64 kg/m^2). Thirty-six subjects had total sperm count <5 × 10^6, forty had 5–20 × 10^6, eleven had 20–40 × 10^6 and nineteen were normozoospermic (>40 × 10^6). Mean±S.D TSH levels were 1.51±0.85 mIU/l; mean testosterone: 4.51±1.81 ng/ml; total sperm count: 20.6±28.5 × 10^6, semen volume: 3.3±1.4 ml; mean FSH: 6.1±4.8 mIU/ml; mean LH: 4.3±2.5 mIU/ml; mean PRL: 7.1±5.1 ng/ml. Total sperm count, semen volume and testosterone levels in relation to TSH levels were

evaluated using Pearson's correlation (age and BMI were also considered as possible confounding factors).
Results
A weak correlation was found between logTSH levels and the log total sperm count with marginal statistical significance ($r=+0.16$, $P=0.09$). The other parameters showed no correlation with TSH.
Conclusions
We noticed a weak association between TSH levels and sperm count. With larger series maybe this relationship can be stronger. Further studies are needed to draw more reliable conclusions that would be useful in daily clinical practice.

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EP383

Could omentin concentration be an indicator of cardiovascular risk in PCO-S

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Introduction
There have been described that about 50% of women diagnosed with PCO-S, present lipid metabolism disorders, insulin resistance and incorrect blood pressure. They suffer not only from fertility disorders, but also present a risk of metabolic complications such as: obesity, type 2 diabetes and hypertension, which increase diet-related cancers and cardiovascular risk.
Aim
To explore if serum omentin concentration could be an indicator of cardiovascular risk in PCO-S, lipid panel, SBP, DBP and QUICKI values, also predisposing CVD factors were assesed.
Material and methods
33 women, aged 18-39, with PCO-S were included in the study. The patients were hospitalized in Endocrinology City Hospital in Piekary in 2015-2019. The predisposing CVD factors were: BP different from <120/80 mmHg, TC > 190 mg/dl, LDL > 135 mg/dl, HDL < 50 mg/dl, TGC > 150 mg/dl, HOMA-IR > 1.5, glucose > 100 mg/dl, BMI > 24.9, smoking and reduced physical activity and assigned 1 point for every existed factor. Anthropometric measurements were conducted and blood parameters from the medical patients records were taken. To determine the serum omentin concentration ELISA method was used. Statistically significant value $P<0.05$ was assumed.
Results
The average serum omentin concentration in examined women was 274 ng/ml (± 78), TC concentration was 193 mg/dl (± 45), BP value 121/76 mmHg (± 12) and QUICKI value was 0.3 (± 03.05). Statistically significant negative correlation between serum omentin concentration and SBP and DBP was shown ($P=0,03$; $P=0,002$). As the concentration of omentin increased, an increase in QUICKI value was observed ($P=0.001$). Negative correlation was observed between serum omentin concentration and predisposing CVD factors ($P=0.008$). There were no correlation between serum omentin concentration and lipid panel values.
Conclusion
Serum omentin concentration could be an useful tool to demonstrate the risk of CVD in women with PCO-S. Further studies in a larger group are required to confirm the CVD risk diagnostic value of omentin.

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EP384

Cardiac defects in turnerian patients

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Introduction
Turner syndrome is one of the most common chromosomal abnormalities, with a reported prevalence of one in every 2.500 live-born girls. The phenotype includes short stature, primary ovarian failure, and other characteristics resulting from the consequences of fetal lymphedema and skeletal abnormalities. Turner syndrome can be associated with multiple defects: cardiovascular, renal, auditory, and skeletal. The aim of our study was to detect the prevalence of cardiac defects in our Turner patients.
Material and method
This is a retrospective descriptive study realized in 15 patients followed for a Turner syndrome at the Endocrinology-Diabetology and Nutrition Department of the Mohammed VI University Hospital Center of Oujda, Morocco.
Results
The mean age of diagnosis was 12.2 ± 13 years [3–41 years]. 40% were diagnosed in adulthood. The reason for consultation was dominated by short stature in 40% of cases with a height under -3DS in 60% of patients, followed by primary amenorrhea in 26.7% of cases. Six patients had a history of low weight for gestational age. Dysmorphia was present in all of our patients. Cardiac exploration revealed a median heart with levocardia and situs salitus in 3 patients, one of whom also had aortic bicuspid and the other had mitral leakage. The analysis of caryotype objectified two cases of monosomy, and one case of mosaic.
Conclusion and discussion
Cardiac abnormalities are common in Turnerian girls and are found in about 50% of cases. Early identification of congenital cardiac defects is crucial as they are a major cause of morbidity and mortality in Turner syndrome, hence the importance of systematic screening at diagnosis followed by strict long-term monitoring.

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EP385

Hyperandrogenism caused by a leydig cell tumor of the ovary: A case report

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Introduction
Leydig stromal cell tumors are a subtype of steroid tumors that make up to less than 0.1% of the ovarian tumors. These neoplasms can affect women from all ages but are more frequent after menopause, being usually unilateral, benign and small sized. In around 75% of cases, these tumors produce androgenic hormones, causing oligomenorrhea and virilization.
Case report
A 39-year-old woman, nulligravid, with complains regarding androgenic alopecia, acne and hirsutism, associated with weight gain for the last 8 months. She referred menstrual irregularities with oligomenorrhea after stopping taking oral contraceptive 9 months ago. The objective examination revealed an androgenic facies and alopecia, dorsocervical adiposity, acanthosis nigricans and clitoromegaly. Blood analysis revealed total testosterone 10.52 ng/ml (0.06–0.82), estradiol 41.8 pg/ml (1.3–266), androstenedione 5.13 ng/ml (0.3–3.3), DHEA-S 246.6 µg/dl (60.9–337.0), prolactin 32.7 ng/ml (4.8–23.3), LH 0.61 mUI/ml (2.4–12.6), FSH 0.87 mUI/ml (2.1–12.6), with normal thyroid function and free 24 h urinary cortisol. The gynaecological transvaginal ultrasound revealed an heterogenous solid lesion in the left ovary with 15 × 15 × 16 mm of smooth margins. A pelvic magnetic resonance showed globosity of the central stroma of the left ovary and the abdominal CT did not reveal any adrenal pathologic findings. The patient was submitted to laparoscopic left adnexectomy that proceeded without complications. A microscopic analysis of the surgical specimen revealed

a Leydig cell ovarian tumor. During the follow-up medical consultations 1 month and 4 months after surgery, there was a notorious improvement of the clinical hyperandrogenism (hirsutism, androgenic alopecia), with regularization of the menstrual cycles and normalization of the serum androgens.
Conclusion
Ovarian tumors that produce androgens are a diagnostic challenge that must be considered in the differential diagnosis of severe hyperandrogenism. This case report of a woman presenting with virilization signs, shows the importance of undertaking a careful gynecological exam, followed by measurements of serum androgens and abdominopelvic imaging to exclude androgen producing tumors of the ovaries or adrenals. The virilizing tumors of the ovaries are surgically treated, usually having good prognosis.

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EP386

A nonpalpable leydig cell tumor and gynecomastia: A case report

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Introduction
Leydig cell tumors (LCTs) are uncommon neoplasms arising from gonadal stroma, accounting for 1–3% of all testicular tumors in adults. The etiology of LCT remains unclear. About 25% of LCTs secrete predominantly estrogens, which produce gynecomastia.
Observation
We report a case of a 53-year-old male patient who sought evaluation for bilateral gynecomastia. He had a long-term use of amitriptyline and benzodiazepine. The physical examination of the testicles was normal. A left testicular tumor was found on echographic analysis. The serum germ cell tumor markers showed no significant abnormalities. Radical left orchidectomy was performed by an inguinal approach. The anatomopathological study disclosed a LCT as the immunostaining showed that the tumor cells were positive for inhibin and calretinin. There were no cytological signs of malignancy or evidence of metastasis. Two years and a half after the surgery, the follow-up CT-scan did not reveal any local recurrence and distant metastases. Hormonal investigations showed moderately elevated estradiol level and low level of testosterone at 2.3 ng/ml, while tumor markers AFP and β-hCG were still negative. The gynecomastia persisted as well.
Conclusion
In the last few years, the incidence of LCTs seemed to increase well above the literature predictions. A hormonal study and scrotal ultrasound evaluation should be performed even in the absence of palpable testicular tumors. Complete recovery of both endocrine and exocrine testicular function is not guaranteed. This may be secondary to a slowly reversible (or irreversible) estrogen-induced damage to tubular and leydig cells.

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Clinical and etiological aspects of hirsutism

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Introduction
Hirsutism is a condition featuring an excessive growth of terminal hair at the woman's androgen-dependent areas, which develops in a distribution model similar to that of men. It is one of the most common disorders in women during reproductive age. It affects up to 1 in 7 women. The objective of this work was to study the clinical and etiological aspects of hirsutism.
Material and methods
This is a retrospective descriptive study involving 59 patients followed for hirsutism in the endocrinology-diabetology and nutrition department.
Results
We collected 59 patients with a mean age of 24.8±6.9 years. 28.8% had a family history of hirsutism. The history of male stillbirths was reported in 12.5% of cases. Forty percent of patients had onset symptoms at puberty. Hirsutism was severe in 44.1% of cases, moderate in 35.6% and light in 20.34% of cases, with an average of Férriman and Gallway score at 17.95±6.32. It was associated with acne in 44.07% of cases, seborrhea in 16.95% of cases, and menstrual disorders in 66.1% of patients. Four patients presented signs of virilization: clitoridomegaly (1 case), frontal gulfs with muscular hypertrophy (2 cases), alopecia (1 case). Overweight was found in 32.2%, while obesity was found in 25.42% of cases. The results showed elevated testosterolemia in 35.09% of cases with a mean of 1.10±1.93 ng/ml. The etiologies were dominated by polycystic ovarian syndrome (PCOS) (60.34%), followed by idiopathic hirsutism in 24.14% of cases, and cushing disease in 8.62% of patients, adrenal tumour (1 case), 21 hydroxylase block (1 case), 11 betahydroxylase block (1 case), and drug use (1 case).
Conclusion and discussion
Polycystic ovarian syndrome is the most common cause of hirsutism in our study, which is consistent with the data reported in the literature. Hirsutism is a frequent reason for consultation; it not only reflects circulating androgen levels, but is also influenced by peripheral androgen metabolism, the sensitivity of the hair follicle to androgens, and insulin resistance. Women suffering of hirsutism often have low self-esteem and altered quality of life, which can lead sometimes to depression, hence the interest of a global therapeutic and psychological management.

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EP388

Probable role of KLK3 in menstrual cycle of young women

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Introduction
Recent studies report the presence of KLK_3 in women serum, KLK_3 is excreted by Skene glands, it is involved in the production of cervical-vaginal fluid (CVF). Activation of KLK_3 is pH depending, it has been hypothesized to have antimicrobial, immuno-regulator activity and vaginal and cervical epithelial desquamation. We intend to verify if KLK_3 is present in female serum, in which menstrual cycle phases KLK_3 increases and its main role.
Materials and methods
They were enrolled voluntary young women aged between 21 and 44 years with specific requirements: no professionally exposed, no alcohol, no smoking, no drugs, no use of oral contraceptives for at least 2 years and regular menstrual cycles.To the participants was asked the age of the menarche, if they are nulliparous/multiparous and if they have had spontaneous/volunteer abortions. BMI (body mass index) and the Ferriman-Gallwey score were calculated. Blood samples were taken in three periods of the cycle (days: 5/6; 12/13; 19/20) for the plasma assay of total KLK_3 and in the third sample the Progesterone test was performed. The method used is "Access Hybritech PSA" test. The total KLK_3 values are expressed in ng/ml.
Results
KLK_3 showed a non-homogeneous behaviour, in fact out of 82 participants, 27, equal to 32.9%, can't be measured in any of the three samples, 55, equal to 67.1% gave values measurable. The comparison of total KLK_3 values with the anamnestic data and semeiotic evaluations didn't give significant correlations. We subdivided the Progesterone values into two bands: band A with Progesterone values >14.5 ng/ml and Band B with Progesterone values <14.5 ng/ml. In band B, from the values of the first sample there is a decrease in the second sample and then a constant decrease in the third one. Instead in band A, there is a continuous increase. The curve of the total KLK_3 values for multiparas is comparable to that of Progesterone (band A). This could demonstrate an interaction between the total KLK_3 and Progesterone.
Conclusion
The transition between the ovulatory and the lutein phase is the key to understanding the quality of ovulation. Measuring KLK_3 in the days before ovulation, it would give us indications on how ovulation will be. KLK_3 values variation, as in the Profile A, indicates an excellent ovulation that could be different from the one with decreasing values (Profile B). In fact, the curve of KLK_3 in Profile A is comparable with that of the multiparas.

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The genetic background of coagulation factors can predict the presence of oligo- or amenorrhea in girls with anorexia nervosa: A pilot study

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Introduction.
The aim of this study was to investigate the association between the genetic background of coagulation factors and the presence of oligo- or amenorrhea in adolescent girls diagnosed with anorexia nervosa compared with controls.
Patients and methods
A total of 40 adolescent girls diagnosed with anorexia nervosa aged 14–17 years, as well as 10 age-matched girls, were included in the study. We recorded anthropometric parameters and calculated body mass index (BMI) z-scores adjusted for age, as well as duration of amenorrhea. Blood samples were obtained for genotyping and hormonal assessment. Genetic polymorphisms of MTHFR (methylenetetrahydrofolate reductase C677T and A1298T), GpIIb/IIIa (glycoprotein IIb/IIIa) and prothrombin were investigated.
Results
Presence of the GpIIIa Leu33/Pro was evident almost solely in the subgroup of anorexic girls (cases vs controls, 27.6% vs 5.9%, P-value = 0.073). Anorexic girls had higher odds than controls to carry: i) the GpIIa leu33/pro or G20210A mutation (34.5% vs 5.9%, P-value = 0.028) ; ii) the GpIIIa Leu 33/Pro mutation or the MTHFR A1298C (62.1% vs 29.4%, P-value = 0.032). Furthermore, girls with oligo- or amenorrhoea compared with girls presenting with normal menses had significantly higher prevalence of: i) the GpIIIa Leu33/Pro mutation (30.3% vs 5.9%, P-value = 0.048) ; ii) GpIIIa Leu33/Pro or the G20210A mutation (36.4% vs 5.9%, P-value = 0.020) ; iii) any mutation from the panel, consisting of the GpIIIa Leu33/Pro or MTHFR A1298C (60.6% vs 29.4%, P-value = 0.037). Logistic regression analysis proved that the presence of any mutation from the panel, consisting of G20210A or the GpIIIa Leu33/Pro mutation, as well as levels of estrogen, predict the development of amenorrhoea (OR 15.618, P-value = 0.043), in a model adjusted for age, BMI z-score and diagnosis of anorexia nervosa.
Conclusions
Genetic background of coagulation factors can predict the presence of oligo- or amenorrhea in girls diagnosed with anorexia nervosa.

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Quality of life questionnaires in PCOS- the impact of hirsutism

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Introduction
Polycystic ovary syndrome is the most frequent ovarian dysfunction during the reproductive period. Its presence significantly impacts on the final scores of various Quality-of-Life (QoL) questionnaires. This pilot study aims to analyze the impact of hirsutism (H), as the component of PCOS, on the scores of determined generic (General Health Questionnaire-12, GHQ12) and disease-specific questionnaires (Polycystic Ovary Syndrome Questionnaire, PCOSQ) in PCOS subjects.
Material and methods
A pilot cross-sectional study involved 30 age- and BMI-matched subjects recruited at the Outpatient Endocrinology Department. The examinees are divided into two groups depending on the H- distribution score, determined by Ferriman-Gallwey (FG) scale (group 1: FG ≤ 8 and group 2: FG > 9). Examinees independently fulfilled both questionnaires (GHQ12 and PCOSQ), and the responses are rank-transformed and presented as scores. Statistical analyses were performed by SPSS for Windows 18.0.
Results
Mean GHQ12, overall, and H-domain of the PCOSQ score of the study population were 12 ± 7 (2–26), 5 ± 1 (2–7), and 6 (2–7), respectively. GHQ12 and overall PCOSQ scores statistically negatively correlated as well as the H-domain of PCOSQ and FG scores. Concerning the study groups, the GHQ12 score is higher in the FG > 9 group along with PCOSQ and H domain of PCOSQ scores, which are less in FG > 9 comparing to FG ≤ 8 group.
Conclusion
Our results suggest that H associated with PCOS directly impacts on general and disease-specific aspects of QoL. Therefore, it is of particular interest to assess the patient's attitude about H presence.

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EP391

Diagnostic value of anti mullerian hormone for detecting polycystic ovary syndrome in Tunisian morbidly obese women

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Introduction
The level of anti-Mullerian hormone (AMH) is considered by several authors as a marker of polycystic ovary syndrome (PCOS). However, data are lacking regarding the real role of AMH and its cut-off value for predicting the existence of PCOS in women with morbid obesity.
The aim of this study was to analyze the performance of the AMH assay in the diagnosis of PCOS in women with morbid obesity.
Patients and methods
We conducted a cross-sectional study including 50 women of reproductive age with morbid obesity. Each patient underwent a clinical examination, biological and hormonal assays and an ovarian ultrasound between the third and fifth day of the menstrual cycle. PCOS was diagnosed according to the Rotterdam criteria.
Results
Participants had an average age of 34.2 ± 7.5 years. PCOS was diagnosed in 20 women (40%). No statistical differences were found between women with and without PCOS regarding age and anthropometric parameters. The mean AMH level was significantly higher in women with PCOS (3.4 ± 3.6 ng/ml vs 1.3 ± 1.2 ng/ml, P = 0.01). It was positively correlated with the Ferriman and Gallwey score (r = 0.49, P = 0.01), total testosterone levels (r = 0.52, $P < 10^{-3}$) and the LH/FSH ratio (r = 0.29, P = 0.04). Furthermore, AMH level was not correlated with anthropometric parameters, nor the HOMA index, nor the volume of the ovaries nor the number of antral follicles. The area under the ROC curve of AMH in the diagnosis of PCOS was 0.71 ± 0.07, P = 0.01. An AMH level ≥ 5 ng/ml had a sensitivity of 20% and a specificity of 100%. In contrast, an AMH level ≥ 1 ng/ml was significantly associated with PCOS with an Odds Ratio of 4.9 (P = 0.02).
Conclusion
Our results showed an association between PCOS and AMH level in women with morbid obesity. However, specific thresholds for this population must be determined in order to improve the sensitivity and specificity of this hormonal marker.

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EP392

Turner's syndrome: Clinic, therapeutic and evolutive particularities in a tunisian center

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Introduction
Turner's syndrome (TS) affects 1/2500 female births and it is characterized by growth retardation, dysmorphic syndrome and gonadal dysgenesis. Our objective was to describe the clinical, therapeutic and evolutive features of Tunisian patients with TS.

Patients and methods
It was a retrospective study including 23 patients with TS diagnosed between 1993 and 2019.We noted clinical, therapeutic and evolutive data for each patient.
Results
The average age at diagnosis was 17 years (10–33 years). The karyotype showed a 45 × 0 monosomy ($n=13$), a mosaicism without structural abnormality ($n=6$) or a mosaicism with structural anomaly ($n=3$). Our patients consulted for growth retadration ($n=9$) and amenorrhea ($n=14$). Twenty-eight percent of them had an history of otitis. Dysmorphic syndrome was present in 20 patients with a pathological cardiovascular examination in 2 patients. Hypothyroidism was noted in 6 patients, celiac disease and hyperthyroidism (Graves' disease) in one patient. Growth hormone (GH) therapy was started in 9 patients, for other patients advanced age was a limiting factor for treatment. The final height was greater in the patients having received GH treatment ($P=0.01$). The mean age of induction of puberty was not delayed in the patients who received GH ($P=0.384$). Spontaneous menarche was noted in one patient who had a mosaic karyotype without structural abnormalities.
Conclusions
The diagnostic of TS is very late in our country. GH treatment has a significative effect on the final height but it must be established in childhood. We have to think about TS in case of dysmorphic syndrome or statural delay in young girls.

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EP393

Acquired nonreversible hypogonadotropic hypogonadism and impaired wound healing in diabetic foot syndroma of type 2 diabetic patient - Case series

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Introduction
The fact that up to 33% with type 2 diabetes develop hypogonadotropic hypogonadisms (HH), are still not catching enough attention. More futher ''the 5-year mortality of somebody who has got diabetes, who has had a myocardial infarction is actually lower than the diabetic patient who has developed a diabetic foot ulcer, which is around 48%''.
Case description
We describe male patient, 47 y. (on 2016y), newly diagnosed type 2 diabetes mellitus (already established background retinopathy; BG 18 mmol/l, pH 7.45) and amputation of digit V (infection cum necrosis). BP 170/90 mmHg, HR 110/min, on CW doppler noncompressible aa., in B mode calcified atherosclerotic plaques. BH 153 cm, BW 46.2 kg (BMI 19.6 kg/m2). CRP 116.8 mg/l, HbA1c 9.6%, TG 1.71, HDL chol. 0.81, cholest 4.91 mmol/l, US abdomen steatosis hepatis. 3 yrs ago he was anaemic. FSH 3.1 IU/l, LH 2.3 IU/l, testosteron (T) 5.82 nmol/l. In the next 3 months all small digits (II-V) were amputated, but still with nonhealed wounds. On twicely given premix insulin HbA1c 6.1%. In the time period 2016–2020y.: T 8.9±3.1 nmol/l and estradiol (E) 33.75±3.3 pg/ml while on clomiphene Tx T 21.9±4.3 nmol/l and E 56±8.5 pg/ml. On clomiphene, maximal FSH have been 8.1 and LH 5.6 mIU/ml. During 2017.y. wound on his foot heald. The only improved symptom of normal T level has been better erectile function (''rigidity of penis''). During low testosterone, a distinctive redness of cheekbones, and during both phases, testicles were with normal size and hardness. As a control patient we used Type 1 diabetic, with diabetic ketoacidosis, as a result of 4 day omission of insulin therapy, in december 2019. 7th day after admitance in Clinic T 6.9 nmol/l, FSH 4.1 and LH 8.15 miu/but on 14th day T rised lspontaneously on 14.27 nmol/l (FSH 7.57 and LH 6.86), E 25 and 35 pg/ml.
Discussion
We conclude that our patient do have insulin resistance of neuronal cells that secrete GnRH but these cells are functional when we eliminate suppressive effect of estrogen by clomiphen. At the periphery it might have been positive effect of estrogen on wound healing in diabetic foot syndroma. Mild anemia that preceded diabetic foot wounds might be in relation to low testosteron. In second case, simple insulin therapy reestabished the function of neuronal cells that secrete GnRH.

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The relationship between TRAB and inhibin-B in male with graves disease

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Introduction and aim
Graves' disease which is the most common cause of hyperthyroidism is an autoimmune disease presenting with goitre, orbitopathy and dermopathy. The disease is caused by stimulant type TSH receptor antibodies (TRAB). TSH receptor (TSHR) has been shown in different tissues other than thyroid. Testis is one of the extrathyroidal tissues with TSHR. The aim of this study was to investigate relationship between TRAB and inhibin-B, which is an indicator of spermatogenesis.
Materials and methods
After approval of the Clinical Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital, 53 male patients who were admitted to the outpatient clinics aged 18 to 65 with Graves disease positive for TRAB and 34 male controls with no infertility problems, autoimmun diseases and medications whic may affect Hypotalamo-pituitary-gonadal axis were included the study. Sociodemographic data form was applied to all patients included in the study and TSH, fT3, fT4, Anti-TPO, Anti-Tg, TRAB values were recorded. For inhibin B assay, 5 ml venous blood was collected in a plain bottle without anticoagulant between hours 08:00–11:00 and serum was separated by centrifugation. The serum aliquots were stored at -80 °C untill analysis. Inhibin-B studied with ELISA (E-EL-H0313 Detection Range: 7.81~500 pg/ml, Sensitivity: 4.69 pg/ml)
Results
Mean age was 39.5±11.8 years in patient group and 40.17±12.1 in control group. Mean duration of disease was 31 months. Mean TSH was 3.5±13.8 this is because of high TSH values of hypothyroid men among patients and median TSH was 0.02 in patient group. Mean TSH was 1.3±0.69 in control group. There were 35 hyperthyroid, 14 euthyroid, 4 hypothyroid men in patient group and all men in control group were euthyroid. Serum inhibin-B was negatively correlated with body mass index (BMI) ($r=-0.217$, $P<0.01$) and positively correlated with existing of thyroid nodules ($r=0.255$ $P<0.05$) in patient group; on the other hand we did not observe relation between TRAB, TSH, Anti-TPO, Anti-Tg, fT4, fT3 and inhibin-B in patient group. Studies demonstrated that inhibin-B is lower in TRAB positive Graves patients than control group ($P<0.0001$).
Conclusion
This study showed inhibin-B is significantly low in TRAB positive Graves patients but no significant relationship between TSH, fT3, fT4, TRAB, duration of disease and inhibin-B. Therefore, all patients with Graves disease should be consulted on their reproductive health.

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EP395

Leydig cell tumor of the ovary: a rare cause of postmenopausal virilization

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Introduction
Postmenopausal virilization with acute onset and rapid progression requires a thorough investigation for the presence of adrenal or ovarian tumor. We present here a challenging case of a radiologically not visible and rare androgen-hypersecreting ovarian tumor.
Case report
A 71-year old postmenopausal woman presented to our department for the investigation of terminal hair growth, of recent onset and rapid progression, on the upper lip, chin and thighs. Physical examination revealed hirsutism

(Ferriman-Gallway score of 11) and signs of virilization with clitoromegaly. On hormonal evaluation she had high levels of serum testosterone (4 ng/ml), while androstenedione (Δ4-A: 1.5 ng/ml), dehydroepiandrosterone sulfate (DHEA-S: 150 µg/dl) and 17 (OH) progesterone (17 (OH) PRG: 1 ng/ml) were within nomal range. MRI imaging of the pelvis was unremarkable, while adrenal CT imaging demonstrated a small left adrenal hypodense lesion of 1 cm diameter. She underwent laparoscopic left adrenalectomy and histopathology was indicative of a non-secreting adrenocortical adenoma. Postoperatively, clinical and biochemical hyperandrogenism persisted. Subsequently, she had a laparoscopic bilateral salpingo-oophorectomy and histopathological examination revealed the presence of a small Leydig cell tumor of the right ovary of approximately 1.2 cm diameter, with no features indicating malignant potential. Postoperatively, serum testosterone levels dropped and were within normal range (0.025 ng/ml) and remain so at her 3 month follow up accompanied by clinical improvement.
Conclusion
Hyperandrogenism in the menopause may be challenging. Rapid development and the presence of virilization signs are usually indicative of a tumor of either adrenal or ovarian origin. When the tumor is radiologically not visible and the adrenal origin of the hyperandrogenism is excluded, laparoscopic oophorectomy might be needed, despite the negative radiological results. Sertoli-Leydig cell tumors are extremely rare; typically, they are unilateral and confined in the ovary. Unlike our case, most patients are premenopausal and the tumor size is large. Prognosis relies on the degree of differentiation of the tumor and is usually favorable.

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EP396

Unusual manifestation of an endocrine-active testicular tumor

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Introduction
Leydig cell tumors (LCT) are rare testicular tumors, characterized by mostly benign etiology. Due to their secretory activity androgen- and/or estrogen-excess can occur.
Case report
A 42-year old patient with recent history of cerebrovascular incident was admitted to the hematology department for diagnostic work-up of new-onset erythrocytosis (hemoglobin 185 g/l [reference 127–163], hematocrit 0.53 [0.37–0.46]). Myeloproliferative neoplasia and other common causes of secondary erythrocytosis (i.e. obstructive sleep apnea, smoking) could be excluded. Remarkably, gonadotropin levels were suppressed on repetitive measurements (LH <0.1 U/l [1.7–8.6], FSH <0.1 U/L [1.5–12.4]). Total testosterone-/SHBG levels were in the mid-normal range (17.9 nmol/l [8.64–29] and 38.6 nmol/L [18.3–54.1], respectively) and estradiol was high-normal (154 pmol/l [41.4–159]). DHEA-S, androstendione, 17-OH-progesterone, AFP, beta-HCG and LDH were normal. The patient denied use of anabolic steroids and biochemical features of steroid abuse (i.e. low SHBG- and HDL-levels) were absent. Clinical examination was normal without gynecomastia, normal pattern of secondary hair and normal-sized, bilaterally descended testes without a palpable mass. Three months after initial presentation estradiol levels rose slightly above the upper limit of normal (198 pmol/l) whereas LH/FSH remained suppressed. Testicular ultrasound found a nodular structure of 1.5 cm in diameter. Tumor enucleation was performed, histologically proving Leydig cell tumor (LCT) without signs of malignancy. Postoperatively, hormone metabolism and hematocrit normalized completely during the following months.
Comment and conclusion
Up to 30% of LCT are associated with endocrine hypersecretion leading to a variety of clinical (i.e. gynecomastia, erectile dysfunction and loss of libido) and laboratory (i.e. erythrocytosis) findings which can gradually evolve–as seen in our patient. LCT exhibit specific patterns of endocrine alterations: enhanced aromatase activity leading to higher intratesticular and peripheral estradiol concentrations and secretion of inhibin causing a decline in FSH. However, most of the patients presenting preoperatively with testicular LCT have low-normal but unsuppressed LH-/FSH-levels. In our case the initial finding of suppressed gonadotropins, normal testosterone/estradiol and severe erythrocytosis is striking and the presence of unmeasured paraneoplastic secretion of other sex-steroids with LH-/FSH-suppressing and hematopoiesis-stimulating properties has to be postulated.

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The autoimmune profile of turnerian patients

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Introduction
Turner Syndrome is a genetic disorder linked to the total or partial absence of an X chromosome. The clinical presentation is heterogeneous, associating a small stature with a dysmorphic syndrome that varies from one person to another.
The aim of this study was to determine the prevalence of autoimmune diseases in our Turnerian patients.
Material and method
This is a retrospective descriptive study collecting 15 cases of Turnerian patients followed in the Endocrinology-Diabetology and Nutrition Department of the Mohammed VI University Hospital Center of Oujda, Morocco.
Results
The mean age of diagnosis was 12.2 13.1 years. Only 33.3% of cases were diagnosed in childhood. Short stature was objectified in 40% of cases, followed by primary amenorrhea in 26.7% of cases. Four patients had peripheral hypothyroidism (26.7%). Hashimoto was noted in 2 cases. Celiac disease was diagnosed in 2 patients, and type 1diabetes in one case. Psoriasis was diagnosed in one patient.
Conclusion and discussion
Autoimmunity has been recognized as one of the most important characteristics of Turner syndrome. Turner patients have an increased risk of developing in particular: Hashimoto's autoimmune thyroiditis, celiac disease, type 1 diabetes, psoriasis and rarely Basedow's disease. The results of our study are consistent with those reported in the literature; the frequency of these pathologies requires systematic screening at the time of diagnosis and during surveillance.

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EP398

Prevalence and awareness of anabolic-androgenic steroids use among male bodybuilders in the eastern province, saudi arabia

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Purpose
The use of anabolic androgenic steroids (AAS) to improve fitness and increase muscle mass is widespread among athletes. Information regarding self-administered AAS used to enhance athletic performance or improve physical appearance is sparse and poorly documented in Saudi Arabia. The purpose of this study is to investigate the prevalence and motivation of AAS use and knowledge of its adverse effects among fitness centres visitors in Eastern Province, Saudi Arabia.
Methods
A cross-sectional survey was conducted among 541 male bodybuilders visiting fitness centres in the Eastern Province region of Saudi Arabia. Information on demographics, use of AAS and awareness about its adverse effects were collected using a self-administered questionnaire.
Results
The prevalence of AAS among bodybuilders in Eastern Province was 21.3%. The percentage was highest among those in the 21–30 years age group and those who received higher education (63.8% and 66.4% respectively). The most common types of AAS used were Oxandrolone (Anavar) (61.9%), Methandienone (Dianabol) (46%) and Nandrolone-decanoate (Deca-Durabolin) (45.1%). Participants were not aware of the adverse effects of anabolic steroids use. Side effects experienced by 77% AAS users; includes depression in 47%, acne was reported in 32.7%, hair loss in 14.2% and sexual dysfunction in 10.7%. On the other hand, 88.5% of the AAS users reported fast muscle gain, and more than half of them noticed increasing in

muscle strength. Despite experienced some side effects, 40% of the users has recommended others to use anabolic steroids.
Conclusion
AAS abuse is a common problem among young bodybuilders associated with lack of knowledge regarding its adverse effects. Health educational programs are needed to increase the awareness of the community towards this problem. The information provided in this study should help clinicians to develop appropriate intervention strategies for AAS abuse.

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EP399

The role of E2/P ratio in the etiology benign breast disease and mastopathy

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The aim of the study was to assess the role of the estradiol and progesterone relationship during the late luteal phase and the occurrence of fibrocystic breast disease (FBD). The concentration of E2/P was measured in the group of women with FBD as study group and healty control group. All women had regular ovulation cycles. Blood samples for E2, P and prolactin determination were obtained in the morning at 8 am on days 21 and 24 of menstrual cycle. Significant mastalgia and mastodynia history in women with FBD was obtained with yes or no questionnaire. FBD diagnosis was confirmed with ultrasound. In the control group, a reduced E2/P ratio was noticed from day 21 to day 24 of the cycle, which was not recorded in the group of women with FBD (study group). Even the slightest disturbance of the E2/P ratio may contribute to the occurrence of benign breast disease with clinical manifestations of mastalgia and mastodynia.

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EP400

Efficiency of ceylon cinnamon on insulin resistance parameters in polycystic ovary syndrome

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Introduction
Insulin resistance (IR) is the main pathogenic factor in polycystic ovary syndrome (PCOS) and its complications. Ceylon cinnamon (CC) is an herb with an insulin-sensitizing effect reported in diabetic patients.The aim of our study was to assess the efficiency of CC on the parameters of the IR in patients with (PCOS).
Methods
We conducted a prospective interventional study, we included 13 patients with PCOS diagnosed according to the Rotterdam criteria, having received neither dietetic education nor metformin, and diabetic patients were excluded. At T0, all of our patients had a food survey, anthropometric measurements: weight, height, waist size (WS), to calculate the WS/height ratio (IR indicator), and a biological assessment: Insulinemia and fasting blood sugar to calculate the HOMA-IR index. During the intervention, our patients received a 500 mg capsule of CC (designed and prepared for the study) three times a day, without changing their eating habits and physical activity.
Results
After 8 weeks (T1), we found a significant reduction in the WS/height ratio (Delta=–0.22±0.03 and $P=0.02$), a non-significant decrease in the average fasting blood sugar, going from 5.35±0.54 to 5.26±0.4 mmol/l (P±NS), the average insulinemia decreased from 20.25±11.93 to 18.91±10.54 µ IU/ml, (P±NS), the average HOMA-IR index was reduced from 4.96±3.22 to 2.75±1.88 (Delta of –0.46±2.85 and P±NS).the reduction in the HOMA-IR index was greater but not significant in patients with IR (Homa-IR index ≥ 2.5) at T0, in this group, the HOMA-IR index fell from 6.25±3.08 to 5.51±2.73 (Delta at –0.74±3.44).
Conclusion
These findings can be attributed to the ability of CC to stimulate the translocation and synthesis of GLUT4 at the cellular level, which improves the cellular response to insulin at its target cell level. Further studies are needed to suggest the therapeutic impact of CC in PCOS.

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EP401

Probable role of KLK3 in menstrual cycle of young women

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Introduction
Recent studies report the presence of KLK_3 in women serum, KLK_3 is excreted by Skene glands, it is involved in the production of cervical-vaginal fluid (CVF). Activation of KLK_3 is pH depending, it has been hypothesized to have antimicrobial, immuno-regulator activity and vaginal and cervical epithelial desquamation. We intend to verify if KLK_3 is present in female serum, in which menstrual cycle phases KLK_3 increases and its main role.
Materials and methods
They were enrolled voluntary young women aged between 21 and 44 years with specific requirements: no professionally exposed, no alcohol, no smoking, no drugs, no use of oral contraceptives for at least 2 years and regular menstrual cycles.To the participants was asked the age of the menarche, if they are nulliparous/multiparous and if they have had spontaneous/volunteer abortions. BMI (body mass index) and the Ferriman-Gallwey score were calculated. Blood samples were taken in three periods of the cycle (days: 5/6; 12/13; 19/20) for the plasma assay of total KLK_3 and in the third sample the Progesterone test was performed. The method used is 'Access Hybritech PSA' test. The total KLK_3 values are expressed in ng/ml.
Results
KLK_3 showed a non-homogeneous behaviour, in fact out of 82 participants, 27, equal to 32.9%, can't be measured in any of the three samples, 55, equal to 67.1% gave values measurable. The comparison of total KLK_3 values with the anamnestic data and semeiotic evaluations didn't give significant correlations. We subdivided the Progesterone values into two bands: band A with Progesterone values > 14.5 ng/ml and Band B with Progesterone values < 14.5 ng/ml. In band B, from the values of the first sample there is a decrease in the second sample and then a constant decrease in the third one. Instead in band A, there is a continuous increase. The curve of the total KLK_3 values for multiparas is comparable to that of Progesterone (band A). This could demonstrate an interaction between the total KLK_3 and Progesterone.
Conclusion
The transition between the ovulatory and the lutein phase is the key to understanding the quality of ovulation. Measuring KLK_3 in the days before ovulation, it would give us indications on how ovulation will be. KLK_3 values variation, as in the Profile A, indicates an excellent ovulation that could be different from the one with decreasing values (Profile B). In fact, the curve of KLK_3 in Profile A is comparable with that of the multiparas.

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EP402

Inhibin-B and FSH – the best male fertility report

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Objective
Sperm cells are produced in the testes by the Sertoli cells. These cells produce Inhibin B and they are stimulated by FSH. Can Inhibin B be a good marker of spermatogenesis? Should we use other marker (FSH?, testosterone?)

Design
Prospective study.
Patients
We examined 71 patients with infertility.
Methods
Semen analysis and hormonal analysis was performed. Semen analysis was performed according to World Health Organization guidelines (WHO 2010). Hormone analysis include: FSH (follicle stimulating hormone), LH (luteinizing hormone), testosterone, prolactin, TSH and inhibin B. We analysed the dependencies between semen parameters and hormons, especially inhibin B.
Results
The sperm count was significantly and positively correlated with Inhibin B ($r=0.4$, $P<0.0001$). The Inhibin B was negatively correlated with FSH ($r=-0.6$, $P<0.0001$). The lower was the concentration of inhibin B, the lower was the number of sperm in the semen. There was also a relationship between seminogram and FSH – the higher was the FSH, the lower was the number of sperm. There was no relationship between the number of sperm and the concentration of LH, testosterone, TSH, prolactin.
Conclusions
It seems that we can use the value of inhibin B and FSH to assess the intensity of spermatogenesis. The decreased concentration of inhibin B correlates with the number of sperm (the lower the concentration of inhibin B the lower the efficiency of spermatogenesis) and with FSH (the higher FSH, the lower the sperm count). High levels of FSH and reduced levels of inhibin B clearly indicate impairment of spermatogenic function in addition to the testes. The concentration of testosterone is not good predictor of spermatogenesis. (Inhibin B and testosterone are produced from different types of cells in the testis).
FSH and inhibin-B can be used if the doctor wants to assess spermatogenesis and the patient does not want to perform sperm analysis (for example, in young boys).

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EP403

Aspects of reproductive state in women after kidney transplantation

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Chronic kidney disease (CKD) is a global burden, with prevalence of 11–13%. CKD usually remains asymptomatic until later stages, but is strongly associated with increased risks of cardiovascular morbidity, premature mortality and decreased quality of life. Kidney transplantation (KT) is a treatment of choice for end stage CKD. KT was performed 350 times from dead donor and 6 times from living donor in the GU 'Minsk Scientific-Practical Center of Surgery, Transplantation and Hematology' in 2018. Objective – Evaluate menstrual function and reproductive state in women after KT. Patients' history was collected by interview and physical examination, hormone levels were determined by ELISA. Ethics Committee approved the study. All patients signed written informed consent. Research group includes 34 women of age 36.4±5.8 who had undergone KT within last 6 years. Patients have adequate graft function confirmed by serum creatinine, urea, cystatine C levels and GFR and are observed by nephrologist regularly. Patients get immunosuppressive medications (Medrol-Ciclosporin/Azathioprin/Tacrolimus- Mucophenolate mofetil) in 2 or 3 component treatment regime and had no complications or concomitant diseases at the time of the study. Women who had severe infections, were pregnant or had complications in graft functioning were excluded from the study. Control group consisted of 27 healthy women. Measures showed 27 patients had menstrual disturbances, the most common oligo- and amenorrhea that depended from age and time that a patient had spent on the dialyses. Average levels of estradiol, Ingibin B, Antimullerian hormone, progesterone, LH and FSH measured in the luteal phase were comparable with no significant difference between two groups. Serum prolactin levels were higher in kidney recipients that in controls ($P=0.01$) with the ranges 693.5±267.7 mIU/l (KT) and 510.0±271.8 mIN/l (healthy women). Testosterone and free testosterone levels we significantly lower in women after KT than in control ones. 25(OH)D status remained below recommended threshold in both groups that was explained by the autumn/winter time of the study. Significant difference was found in levels of LH mediana and FSH mediana in the follicular phase. Women after transplantation suffer from irregular menses, hyperprolactinemia, low levels of testosterone. Different hypotheses suggest connection between immunosuppressive therapy, dialyses time, graft function and obtained data that needs further investigation.

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EP404

DHEA in infertility – can you reverse the flow of time?

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We study the impact of the dehydroepiandrosterone (DHEA) by the women with diminished ovarian reserve and very low DHEA-S in the blood.
Patients
We present a description of 7 patients with diminished ovarian reserve (DOR). Patients reported because of problems with getting pregnant. Infertility lasted for several years. The patients disagreed on IVF for ethical and religious reasons. All of the presented patients were diagnosed with diminished ovarian reserve (very low AMH or high FSH, elevated estradiol concentration on day 3 of the cycle). We found also a very low DHEA-S concentration.
Interventions
The patients were given dehydroepiandrosterone.
Main Outcome Measures
After several months of treatment (3–6 months), the patients became pregnant. None of them had procedures for *in vitro* fertilization.
Results
Seven patients gave birth to healthy children. Our experience with DHEA is much bigger, but these 7 cases are very well documented. The obtained results indicate that DHEA supplementation in conditions of its deficiency improves the functioning of the ovaries and increases the chance of pregnancy.
Conclusions
1. In some cases the aging of the ovaries can be delayed by administering of dehydroepiandrosterone (DHEA).
2. This effect occurs specially when the endogenous concentration of DHEA-S is reduced.
3. In the case of reduced ovarian reserve, DHEA-S concentration should be determined.
4. The question remains open as to whether we should not mean DHEA in the blood of infertile men (does DHEA-S deficiency interfere with sperm maturation?)

Table 1 Patients with infertility and DHEA-S below the reference rage.

Ip	Age	Duration of infertility	FSH – 3rd day of cycle IU/ml	AMH ng/ml	Estradiol 3rd day of cycle	DHEA-S ug/dl	Testosteron ng/ml	The result of treatment	After what time of DHEA application did pregnancy appeared?
1	42	6 years	29.9	0.28	72.8	**24.6** (*N* 25.9–460.2)	9 (*N* 14–76)	Birth of a healthy child	3 months
2	34	5 years	20.23	0.46	49.4	**58.5** (*N* 25.9–460.2)	–	Birth of a healthy child	5 months

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EP405

The occurrence of the hypogonadotropic hypogonadism as a prediagnostic finding for HIV Infection in a patient with klinefelter under testosterone replacement therapy

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Background
Hypogonadism is common among human immunodeficiency virus (HIV)-infected men. The actual prevalence remains poorly defined and ranges from less than 10% to over 50% in different studies. Secondary hypogonadism is the most common cause of hypogonadism among HIV-infected men. In hypogonadal HIV-infected men, naive of highly active antiretroviral therapy (HAART), around 75% have secondary hypogonadism due to the suppression of gonadotropins by the active inflammation and disease. Hematologic neoplasias, occurring in 1.6% of Klinefelter patients could develop in the pituitary region. Gonadal and extragonadal germ cell tumours (mediastinal germ cell tumours, teratoma, teratocarcinoma, choriocarcinoma) may occur.
Case presentation
We followed a thirty-five-year-old male patient diagnosed in our Endocrine outpatient department with Klinefelter Syndrome for appropriate replacement therapy with intramuscular testosterone. Nine months following his diagnosis of hypergonadotropic hypogonadism, endocrine laboratory testing revealed suppressed gonadotrophins despite lengthening of periods in testosterone administration. The patient was well-nourished and asymptomatic for a pituitary tumour. The patient reported no opioids abuse or steroids. Serum levels of free testosterone and SHBG were in the normal range when we tested it after 14 weeks from the last administration of testosterone. We excluded the reversible causes of hypogonadotropic hypogonadism. Serum prolactin was in the normal range. Ultrasound of the testis and normal values for HCG, AFP and LDH excluded a germinal tumour. Blood tests were positive for HIV infection with normal CD4 count. The patient started HAART with Triumeq (dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg). Restauration of normal gonadotrophins secretion after ART initiation will explain the HIV-related cause of hypogonadotropic hypogonadism in this patient.
Conclusion
We report the occurrence of the secondary hypogonadism in a Klinefelter patient under testosterone replacement that drove specific tests that revealed an early stage of HIV infection without advanced degrees of immunosuppression (CD4 > 100 cells/mm^3). Undernutrition, severe illness, drugs, pituitary dysfunction, were excluded in our patient. The endocrinologists frequently overlook HIV infection as a cause of hypogonadotropic hypogonadism. Yet, it must be considered between causes of unexplained gonadotrophins suppression in these patients.

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EP406

Idiopathic childhood cliteromegaly: Testosterone gel and its sensitivity

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We present a 37-year-old gentleman (Mr. A) who self-referred to the endocrine clinic for review of his testosterone replacement therapy.
He required testosterone replacement therapy aged 11 years old following surgical removal of underdeveloped testes of unknown aetiology. He was prescribed testosterone injections until the age of 22 years old when testosterone patches were trialled, which he did not tolerate. He commenced testosterone replacement gel (TESTOGEL 50 mg/5 g sachets) with good effect for 15 years. His biochemical hormone profile was in keeping with primary hypogonadism; LH 33.2 U/l [normal range (NR) 1.7–8.6 U/l], FSH 93.4 IU/l (NR 1.5–12.4 IU/l), testosterone 10.5 nmol/l (NR 8.6–29.0 nmol/l), SHBG 57 nmol/l (NR 14.5–48.4 nmol/l) with a free androgen index of 18 (NR 30–150). Genital examination identified prosthetic testicles with an unremarkable examination of all other systems. Despite good replacement with TESTOGEL he sought alternatives due to ongoing medical complications with his 18-month-old adopted baby girl (Child X) who had concurrently been referred to the paediatric endocrinology team with increased downy hair in the pubic region and an enlarged clitoris. Examination by a paediatric endocrinologist identified dark hair in the pubic region and mild clitoromegaly of approximately 1 cm. There was no axillary hair nor breast development. Child X was born weighing 7lbs and healthy. As minimal information was available regarding her genetic background, further investigations were sought. Child X' genetic karyotyping confirmed 46XX (genetically female) without mosaicism. Full biochemical profile included; testosterone 10.5 nmol/l with undetectable androgen precursors, LH, FSH and HCG with an AFP level in the normal range; suggestive of exogenous testosterone exposure. On further questioning, Mr. A confirmed he only applied TESTOGEL to the upper arms and shoulders, washed his hands fully with soap and covered himself with clothes in the morning prior to attending to Child X, in accordance with manufacturing guidance. TESTOGEL was immediately stopped and testosterone injections commenced. Within two weeks, Child X' testosterone levels improved to 4.5 nmol/l and further fell to 0.9 nmol/l a few weeks later. TESTOGEL 50 mg/5 g is licensed for transdermal testosterone replacement in men with hypogonadism due to androgen deficiency. The manufacturer' Summary of Product Characteristics (SmPC) states the percutaneous absorption of testosterone ranges from 9% to 14% of the applied dose. Application of one TESTOGEL 50 mg/5 g sachet produces an average plasma testosterone concentration increase of 2.5 ng/ml (8.7 nmol/l).
Conclusion
Despite following manufacturing guidelines there was still evidence of testosterone transmission. Do we need to advise and educate against light clothing despite adequate hand washing?

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EP407

The long way to unravel the reasons for differences in phenotypes among MEN1 patients

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a monogenic, dominantly inherited disorder caused by mutations in the *MEN1* gene. Unfortunately, the outcome and the patients' prognosis are unpredictable even among members of one family. It seems clear that other factors influence the individual outcome of the disease. However, it is still unclear what kind of factors (genetic or environmental) would be responsible for the observed differences.
Aim
We have planned a number of connected studies that aim at identifying the direction in which the reasons for the observed differences in MEN1 outcomes should be searched for. The aim of this work is to present the first part of this study, which is based on evaluating the patients' genetic background, i.e. the variants in the patients' genomes. This part of our study focuses on classical genetics.
Methods
We performed high-throughput sequencing that encompassed the whole exomes of 16 patients grouped depending on the outcome of their disease. This patient group included first-degree relatives with different outcomes despite a common underlying *MEN1* mutation. Because of the very limited number of patients, the analyses were based on pathways rather than single gene variants.
Results
We present the premise, methods, analyses, and initial results of the first part of our planned multi-step study on the reasons for phenotype differences in MEN1 patients.
Perspectives
In addition to basic genetic factors, the next part of the analyses will encompass also epigenetic and environmental factors, which will be evaluated all together in one final analysis.

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EP408

Preservation of fertility in men with benign and malignant brain tumors

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Brain tumors are on the 3rd place in terms of growth rates of incidence among oncological diseases. By virtue of the improvement of neurosurgical treatment methods, with the use of modern chemotherapy and radiation therapy, the survival of patients with benign and malignant brain tumors is increasing. A significant proportion of patients with such tumors are young

people of reproductive age who are interested in maintaining their fertility. Neurosurgical removal of tumors, which are mainly located in the hypothalamic-pituitary region, as well as the applying of chemotherapy and radiation treatment of malignant brain tumors of any localization may be complicated by the development of hypogonadism and infertility. A simple and reliable method of preserving male fertility is currently cryopreservation of sperm. We recommend carrying out a cryopreservation of sperm in young patients, as well as in patients interested in the reproductive potential:
1) in benign tumors of the hypothalamic-pituitary region (invasive, large pituitary adenomas, craniopharyngiomas, etc.):
– with intact gonadotropic function prior to surgery and a high risk of developing hypopituitarism (including hypogonadism);
– with hypogonadotropic hypogonadism after surgical, radiotherapy or drug treatment during the course of gonadotropin therapy.
2) in the case of malignant brain tumors of any localization:
– before radiotherapy and/or chemotherapy
Neurosurgeons, as well as oncologists, radiologists should inform patients with brain tumors about the possible risk of hypogonadism development, infertility and the possibilities of sperm cryopreservation, which increases the chances of having future genetic progeny.

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EP409

Characteristics of true precocious puberty in children over last three years

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The aim of investigation to examine characteristics of true premature sexual development in children and adolescents over three years.
Material and methods
We observed 9 children with true premature sexual development (including boy – 1, girls –8), which had treatment in the pediatric department of the Center of Endocrinology in the period from September 2016 to July 2018 years. Patients were measured height, weight, considered a lack of growth, weight, performed a palpation of the thyroid gland and an objective examination of sexual development' stages by Tanner.
All patients underwent a set of studies, including the clinical (General blood and urine analysis), biochemical, hormonal (LH, FSH, prolactin, estradiol, progesterone, free testosterone). Besides that, we performed pituitary MRI and ultrasound investigation of endocrine organs.
Results
It was established that growth excess occurred in all (100%) patients examined. Hormonal disorders were characterized by an increase in average levels of peripheral sex hormones on the radiographs of the brush in all children, an advance of bone age of 3–4 years was revealed No changes in brain MRI were detected. In 3 patients, isolated telarch was noted. All patients received dipherelin therapy.
Conclusions
In the structure of premature sexual development in children, true is relatively rare. A special screening is required to identify this pathology in children

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EP410

The prevalence rate of true precocious puberty in children by region of the Republic of Uzbekistan (as of December 1, 2018)

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The aim of investigation to study the prevalence rate of precocious puberty (PP) in children by region of the Republic of Uzbekistan (as of December 31, 2018). The prevalence rate of premature sexual development in children by region of the Republic of Uzbekistan (as of December 1, 2018).
Material and methods
We observed 173 children with true precocious puberty (including boy – 51, girls – 122), which had treatment in regional endocrinology clinics in the period from January 1, 2018 to December, 31, 2018 year. Patients were measured height, weight, considered a lack of growth, weight, performed a palpation of the thyroid gland and an objective examination of sexual development' stages by Tanner. All patients underwent a set of studies, including the clinical (General blood and urine analysis), biochemical, hormonal (LH, FSH, prolactin, estradiol, progesterone, free testosterone). Besides that, we performed pituitary MRI and ultrasound investigation of endocrine organs.
Results
It was established that as of December 31, 2018 in Andijan region was registered 8 children with PP, in Bukhara region – 32, Djizakh region – 5, Kashkadarya region –2, Navoi region–2, Namangan region-2, Samarkand region –11, Surkhandarya region –42, Tashkent region –9, Fergana region –11, Khorezm region –39, Tashkent city – 5 patients.
Conclusions
The largest number of patients was registered in Surkhandarya region.

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Thyroid

EP411

Severe hypothyroidism causing acute ileus and polyserositis

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Introduction
Hypothyroidism is associated with a spectrum of symptoms affecting almost all bodily functions. We present a case of severe hypothyroidism with multiple body cavity effusions, volvulus of sigma creating ileus.
Case report: A 70 year old female was admitted to emergency department with dyspnea, and acute abdominal pain. Physical examination was notable for anasarca, abdominal fluid wave, lower extremity pitting edema, hypotension. She did not have any comorbidities. Anamnesis of hypothyroidism left unknown during admission. Diagnostic CT scan revealed a volvulus of sigma creating bowel obstruction. Ascites, bilateral pleural effusion, cardiac tamponade were also diagnosed. Sigmostoma was applied for decompression of ileus during urgent laparatomy. Pericardial, pleural and peritoneum drainage was performed. Antibiotics were started due to inflammation (CRP 120 mg/l). Abundant secretion from the peritoneum, pleura and pericardium continued. Polyserositis differential diagnostic tests were done: ANCA –negative, AntiDNA 25.2kU/l, albumine 23.2–16.3 (n–35–52) g/l, liquid from pleura, peritoneum and pericardium had no signs of cancer, tuberculosis. Thyroid function tests showed hypothyreosis: TSH 100 (0.4–3.6) mU/l, FT4 0.1 (9–21.07) pmol/l, FT3 1.17 (3.34–5.34) pmol/l, AntiTPO 63.73kU/l (0–3.2). Adrenal insufficiency was denied: ACTH 7.7 (3–14) pmol/l, morning cortisol 441 nmol/l. Ultrasound of the thyroid gland revealed small lobes and isthmus. Treatment with levothyroxine 50 μg/day was started, human albumin transfusions were applied. Expanded anamnesis revealed that patient had been on levothyroxine replacement but had defaulted treatment for 15 years. Following hospital course was uncomplicated with steadily rising dose of levothyroxine from 50 to 100 μg/day. After 26 days of treatment with levothyroxine TSH was still high (87.5 mIU/l), though FT4 reached 6.73 pmol/l. Abatement of ascites, pleural effusion, tissue oedema and pericardial effusion were observed. Patient continued on a maintenance dose of 100 μg/day levothyroxine with regular follow up.
Conclusion
Isolated ascites (< 4% cases), pericardial effusion (3–6% cases) or pleural effusion is not unusual in hypothyroidism. Volvulus and bowel obstruction were also described as probable rare consequences of hypothyroidism. Multiple body cavities effusions, tissue edema, motility dysfunction causing volvulus and acute ileus and all occurring simultaneously due to hypothyroidism is extremely rare. Due to rarity of these conditions, diagnosis is often difficult and delayed.

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EP412

Late-onset endocrine opthalmopathy due to activation of occult Graves' disease in a patient with toxic adenoma treated with radioiodine (Marine-Lenhart syndrome)

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Introduction
Hyperfunctioning thyroid nodules (toxic adenomas) comprise one of the most common causes of hyperthyroidism and are usually treated with therapeutic radioiodine administration (RAI). Coexistence of such nodules with Graves' disease (GD) is a rare disorder (Marine-Lenhart syndrome) with a reported prevalence of approximately 2.7–4.1% in GD patients. We present a rare variant of this condition, featuring the case of a patient with hyperfunctioning nodular thyroid disease and development of post-RAI endocrine opthalmopathy due to activation of occult autoimmune thyroid component with an excessive elevation of thyroid-stimulating autoantibodies (TRAb).
Case report
A 48-year old smoking female patient with newly detected subclinical hyperthyroidism and related symptoms presented for endocrinological evaluation. She reported no signs/symptoms of orbitopathy. The neck ultrasound revealed 3 heteroechoic nodules of the right thyroid lobe; the adjunctive ^{99m}Tc- scintigraphy was diagnostic for a toxic adenoma and functional suppression of the rest thyroid parenchyma. The patient underwent radioiodine therapy with administration of 12.5 mCi J^{131}. Iatrogenic hypothyroidism developed 3 months post-therapeutically and was treated with oral administration of levothyroxine over a period of 5 months before cessation of therapy due to tendency of supplementation-induced TSH suppression. The patient presented after 2 months with bilateral eye-lid swelling and redness, as well as lacrimation. An evaluation of TRAb showed high titers of >40 IU/l (reference range <1.75 IU/l). The patient was treated with selenium administration over a period of 6 months and reported a progressive remission of her eye symptoms. Due to concomitant relapse of overt hypothyroidism she was started on levothyroxine and remained euthyroid under 62 μg daily.
Conclusion
Radioiodine for the treatment of hyperthyroidism due to nodular thyroid disease may trigger endocrine opthalmopathy in terms of autoimmune activation in patients with undiagnosed occult Graves' disease, especially in active smokers. Therefore, an estimation of TRAb should be considered in every patient with a diagnosis of toxic adenoma and thyroid scintigraphy non suggestive for concomitant Graves' disease. In such rare cases, a careful follow-up should be conducted for the early detection of post-RAI orbitopathy and where indicated a prophylactic post-therapeutic corticosteroid coverage should be administered.

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EP413

Treating TSH or patient? A case of misleading TSH in a young patient

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Background
Primary hypothyroidism diagnosis is mainly based on the TSH (thyroid-stimulating hormone) and free thyroxine (T4) levels. Following treatment initiation, the main lab test used for dose adjustment is TSH. However, there could be potential issues with TSH measurement.
Case report
A young lady, 36, presented to our clinic in January 2019, being treated with Levothyroxine 175 mg daily, and having clinical signs and symptoms of thyrotoxicosis: tachycardia, palpitations, excessive sweating, tremor, increased gut motility, hair thinning and nail softening, menstrual irregularities, insomnia. She was also taking Propranolol PRN to reduce the heart rate. Her personal history was unremarkable until Feb 2009, when she was diagnosed with primary hypothyroidism at age 26, based on high TSH, 16.8 mU/l, and T4 not sampled at the time of diagnosis. She started Levothyroxine therapy, 100 mg daily, her TSH was followed up periodically and was high (> 10 mU/l) on multiple occasions, apparently not responding to treatment, leading to Levothyroxine dose escalations.
At the time of presentation to our clinic, she got her thyroid function tests sampled and, despite the abnormal TSH value (5.79 mU/l), the Levothyroxine dose was reduced to 125 mg daily, which led to significant improvement in her symptoms, and she stopped Propranolol completely.
Two months later, her TSH was 4.3 mU/l, we then performed a PEG (polyethylene glycol) precipitation of the sample, and the monomeric TSH was obtained at the level of 0.58 mU/l. Since then, we further reduced the dose of Levothyroxine to 100 mg daily, her last TSH was 3.34 mU/l (normal), and she feels well.
Discussion
Our case reminds of the fundamental principle 'Primum non nocere'.
Treating the blood test result and continuing to increase the dose aiming to normalise the TSH value, without taking into account the clinical presentation, can lead to overtreatment and cause iatrogenic thyrotoxicosis.
We could only hypothesise that the laboratory testing could mislead due to the presence of interfering macromolecules, taking into account that we did not have possibility to perform a gel filtration chromatography, which is considered a gold standard to identify the monomeric TSH. We could speculate that, in some cases, PEG precipitation is a useful tool to identify patients with falsely elevated TSH levels.

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EP414

Myxoedema ascites: An unusual situation revealing Hypothyroidism

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Introduction
Clinical presentation of hypothyroidism is frequently insidious. Of the many non specific clinical signs of hypothyroidism, ascites is one of the less common manifestations reported and the diagnosis is often made late with this condition. Herein, we present the cases of isolated ascites revealing hypothyroidism in order to drow attention to hypothyroidism as an etiology of an unexplained isolated ascites.
Observation
A 61-year-old diabetic women presented with abdominal distention, constipation and ascites of three months duration. On physical examination, blood pressure was 130/70 mmHg and the pulse rate was 80/min. The abdomen was distended with marked ascitic fluid. Neither the liver nor spleen were palpable. The thyroid gland was also not palpable. There were no signs of congestive heart failure and the electrocardiogram was normal. The initial exploration of ascites could not suggest any etiology: hemogram, bilirubin level, Liver function, protein electrophoresis and creatinine level were normal. There was no proteinuria. Viral serologies B and C and immunoassay were negative. The intradermal reaction to tuberculin was negative. The ascites puncture revealed a transparent fluid, its cell count was 141/mm^3 with 95% lymphocytes, its protein concentration was 36.5 g/l and cultures were negative. Both diuretics (spironolactone) and a sodium restricted diet were prescribed with no improvement. Few month later, the patient developed profound weakness, bradycardia (pulse rate 60/min) and hypoacousia suggesting the diagnosis of hypothyroidism. Thyroid function tests showed a low serum FT4 (1.4 pg/ml reference range :6.6–14 pg/ml) and an elevated serum TSH (75 μU/ml: reference ranges 0.2–3.5 μU/ml). The patient was treated initially with levothyroxine (L-T4) 25 μg/day and gradually increased to 200 μg/day. The ascites rapidly disappeared about 1 month and a half after the start of replacement therapy.
Conclusion
Ascites can be an early clinical magnifestation of hypothyroidism. It is rapidly reversible after hormone replacement therapy, therefore evaluation of thyroid functions should be performed in all patients with unexplained ascites.

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EP415

Iodine status in a group of pregnant women with chronic autoimmune thyroiditis having as provenience perimarine area of Romania

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Objectives
Assessment of the utility of supplementing the iodine intake during pregnancy in women with chronic autoimmune thyroiditis (CAT) coming from the perimarine territory of Romania.
Material and method
The study included 28 pregnant women in the first trimester of pregnancy, diagnosed with CAT. The following variables were evaluated: TSH, FT4, ATPO. The iodine status of pregnant women was analyzed by 2 methods: 1 – the value of the urinary iodine concentration (UIC) from the spontaneous urine sample and 2 – the iodine concentration corrected after the urinary creatinine (UIC/Ucr).
Results : Most of the pregnancies came from the urban area (79%). The gestational age between 8 and 13 weeks predominated in proportion of 82%, whilst only 19% of pregnant women were evaluated in the first 2 months of pregnancy. The median value of TSH was 16.22±23.82 mUI/l and for FT4 the median value was 14.70±3.65 ng/ml. Pregnant women with TSH>2.5 mUI/l were indicated for thyroxine replacement therapy. The median UIC in our study was 113, 74 mg/l (insufficient iodine intake according to WHO recommendations<150 mg/l). Adjustment of iodide after urinary creatinine is necessary to eliminate the interference of increased diuresis specific to the pregnancy period due to the increased glomerular filtration rate. The median value of the UIC/UCr ratio was 170, 51 mg/g, placing pregnant women in the category with sufficient iodine intake. It should be mentioned that 2 patients had excessive iodine values (> 500 mg/l), both intermittently taking iodine supplements, the reassessment of iodide investigations after the UIC/UCr report found normal values.
Conclusions
The recommendation of iodine content supplement administration in pregnant women with CAT should be adjusted depending on the level of urinary iodine assessed during early pregnancy. The method of dosing iodine without reporting to urinary creatinine may suggest iodine supplementation in pregnant women without iodine deficiency, with a potential aggravation of thyroid autoimmune pathology. Normal or supplemented iodine intake in the perimarine area of Romania does not, however, exclude individual cases with urinary iodine variations.

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Grave' disease and Systemic lupus erythematosus association

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Introduction
Graves' disease is an autoimmune disease that affects the thyroid gland and leads to a state of hyperthyroidism. This disease is caused by the production of antibodies that bind to and activate the thyroid-stimulating hormone (TSH) receptor. In some cases, Grave' disease may be associated with other organ-specific or systemic autoimmune disorders. One of the most frequent multisystemic autoimmune disorders is Systemic lupus erythematosus (SLE). Many studies have described the association between SLE and thyroïde disease but mostly hypothyroidism. However, a limited number of cases of Graves' disease have been also reported in SLE patients.
Observation
We describe a case of a 29 years old female without a particular medical family history, with a history of two precocious miscarriages who has been diagnosed with LES associated with Sjogren syndrome in July 2019.
The patient presented a deterioration of the general status and a tumoral syndrome, a biological inflammatory status with pancytopenia and complement consumption. The diagnosis was confirmed by the presence of positive antinuclear antibodies. She was treated with Hydroxychloroquine and corticoids.
In August 2019, the patient was addmitted with a fever, tachycardia and a continuous loss of weight that was initially attributed to an acute episode of her disease. We noticed the presence of a minor exophthalmia and fine tremors but there was no palpable goiter.
The hormonal tests showed a status of hyperthyroidism ; a suppressed thyroïde stimulating hormone (<0.15 mUI/l) and a high FT4 level (64.8 pmol/l). Measurement of TSH receptor antibody was positive and the thyroid Ultrasonogram with Doppler showed an heteromultinodular hypervascular gland. The diagnosis of Grave' disease was posed and the patient was treated with Antithyroid drugs.
Conclusion
The clinical manifestations of LES and Grave' disease can be similar. This association even if not frequent should be suspected in the presence of subtle signs of hyperthyroidism. Since both are autoimmune diseases that can have severe complications.

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EP417

Refractory hypothyroidism: What else should be done?

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The treatment of hypothyroidism is straightforward,replacing with orally L-thyroxine(LT4).However,some factors including malabsorption,pancreas and liver disorders,drug interactions,etc.,may impair the absorption of LT4,and cause therapy failures.In these circumstances,high doses of different oral formulae or parenterally given LT4 may be a solution. Here,we present a case of primary hypothyroidism,resistant to high doses of oral LT4 replacement but,responsive parenteral LT4 administration.
Case
A thirty-eight years old female patient with effort precipitated fatigue,constipation and hair loss was admitted to endocrinology clinic in Jan. 2019. History revealed that she had bilateral total thyroidectomy for papillary thyroid cancer in May 2018. She was given radioactive iodine,100 mCi, in July 2018. Physical exam showed that she had a puffy face,dry skin,decreased hair,and bilateral nonpitting pretibial edema. She was not given any other medications that interact with LT4. At the admission,serum levels of her thyroglobulin,anti-thyroglobulin antibody,freeT4, and TSH were 0.20 ng/ml,3.79 IU/ml,<0.40 ng/dl and 175 mIU/ml,respectively. She has been given high doses of oral LT4, 1000 mg/day. Antibodies against endomysium and tissue transglutaminases were also negative. Endoscopic examination of upper gastrointestinal tract and biopsies of the duodenum also showed no abnormality. Echocardiographic examination revealed pericardial effusion but normal cardiac output. Dose of LT4 was increased to 1500 mg/day,and added 25 mg T3 thrice a day. A few days later, serum levels of thyroid hormones and TSH were repeated,still showing high TSH and low T4, and pointing therapy failure. Hence, we decided to begin intravenous LT4 therapy. Intravenously,1000 mg/day LT4 was applied and observed no unwanted effects. Thereafter,400 mg/day LT4 was given for three days. Therapy, then, was switched to another regime consisting of 200 mg/day LT4 intramuscularly once a week. This approach resulted in normalization of serum TSH and T4 levels. Abnormalities on physical exam at the admission also improved significantly.
Discussion
Our case is refractory hypothyroidism since unresponsive to very high doses of oral thyroid hormone replacement,approaching totally 1500 mg/day T4+75 mg/day T3. We were not able to find such a case report, requiring so high doses in the literature. Currently LT4 is available in tablet, soft gel, liquid and ampul formulations,being mostly used oral tablets. However,this treatment is not sufficient in some patients due to a variety of conditions such as autoimmune gastritis,malabsorption,pancreatic and liver diseases,drug interactions,noncompliance to the prescription,etc. In such situations, in which oral liquid or gel formulations are ineffective,parenteral forms of LT4 should be undertaken. Parenteral form of LT4 is, however,not available in every country. Though it is a very rare condition,it causes great challenges for both the patients and the care providers. Therefore,the health authorities of every country should provide parenteral form of LT4.

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EP418

3-iodothyronamine (T1AM) is taken up and rapidly metabolized in cell culture medium only at low concentration

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3-iodothyronamine (T_1AM) is rapidly catabolized to iodothyroacetic acid after few hours by serum proteins. To avoid a rapid metabolism during any treatment, DMEM devoid of FBS has been used, inducing changes in the cell culture environmental. We evaluated the uptake and the metabolism of different concentrations of T1AM, in presence of supplemented medium,

and the presence of 3-iodothyroacetic aldehyde (Ald), a putative intermediate of T1AM catabolism to TA1.
DMEM supplemented with 10% FBS was spiked with T1AM at concentration 0.1–10 μM and provided to NG108–15 cells or U-87 MG (24-well plates). The medium was removed at specific time points (1,2,3,4, 24 h), and media and cell lysates were analyzed by HPLC-MS/MS to evaluate T1AM and TA1. To assess the endogenous production, cells were incubated with DMEM + 10%FBS or human serum without T1AM. To evaluate the presence of Ald, T1AM (100 μM) was incubated with bovine plasma amine oxidase (0.33 mg/ml). After protein precipitation (CAN?? ACN?), samples were centrifuged and supernatants analyzed by HPLC-MS/MS operating in Full Scan mode to detect ions of interest.
In NG108–15 and U87MG cells, in medium, T1AM at 0.1 and 1 μM rapidly decreased and became undetectable after 2–3 h. Differently, in the infusion with 10 μM, T1AM was measurable after 24 h. T1AM was taken up by cells and catabolized to TA1 which was detectable from the beginning of treatment (1 h), exceeding T1AM concentration after 24h. In cells incubated only with medium, neither T1AM nor TA1 were detected, in this way excluding any endogenous production by neuronal cells.
Putative aldehyde ion (m/z 353) was detected in negative ion mode without the formation of TA1. The fragmentation of this ion led to iodine loss, which reinforced the hypothesis that the detected molecule was a T1AM derivative.
In conclusion T1AM was taken up by cells and catabolized to TA1. The detection of the putative intermediate 3-iodothyroacetic aldehyde still needs to be confirmed by further studies.

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EP419

Subclinical hyperthyroidism as a cause of atrial fibrillation

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Introduction
Subclinical hyperthyroidism is a syndrome with vague clinical symptoms. It may cause tachycardia, loss of weight or no symptoms at all. Subclinical hyperthyroidism may occur in middle age and in the elderly. It may be related to the occurrence of atrial fibrillation. Subclinical hyperthyroidism may be the result of an autonomous goiter, may occur in the course of follow-up of hypothyroidism, as the needs for treatment may vary over time and substantially diminish in middle and old age and may occur in the context of autoimmune thyroiditis.
Aim
The aim was to present a cohort of patients presenting with atrial fibrillation who were subsequently diagnosed with subclinical hyperthyroidism.
Methods
A cohort of 31 patients, 20 male and 11 female, aged 48–72 years presented with atrial fibrillation. Levels of blood TSH, freeT_4, freeT_3, anti-TPO ab and anti-Tg ab were measured and a thyroid ultrasonogram was performed.
Results
TSH levels were found to be diminished. FreeT_4 and freeT_3 levels were found to be normal. Anti-TPO and anti-Tg ab were positive in 18 and 15 patients, respectively. In 20 of the group hypothyroidism was diagnosed as the underlying thyroid illness. Treatment was adjusted to the needs of the patients. In 7 of the patients a multinodular goiter was diagnosed. Antithyroid agents were administered in this group. In 4 patients within the cohort autoimmune thyroiditis was diagnosed. After treatment adjustment in the hypothyroid group episodes of atrial fibrillation decreased in frequency and in two of the patients they were almost eliminated. After antithyroid drug administration in the goiter group episodes of atrial fibrillation were attenuated.
Conclusions
Atrial fibrillation may be the presenting symptom of subclinical hyperthyroidism. Subsequent diagnosis and proper management of subclinical hyperthyroidism may aid in the management of atrial fibrillation. We propose that patients with atrial fibrillation should be screened and appropriately treated for an underlying thyroid disorder.

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EP420

Autoimmunity in thyroid nodules referred for FNAB

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Introduction
The aim of the study was to evaluate the relevance of autoimmunity in the cytological results for the thyroid nodules referred to FNAB (fine-needle aspiration biopsy).
Materials and methods
Our study included 590 patients who underwent FNAC in 615 nodules between December 2015 and January 2019. Besides demographic data and routine endocrine investigations (thyroid hormonal status, presence of autoimmunity, the actual or past use of levothyroxine or inhibitors of the synthesis of thyroid hormones), we retrospectively collected data regarding localization, ultrasonographic (US) Ti-RADS (Thyroid Imaging Reporting and Data System) evaluation and Bethesda based cytology findings. We analysed the obtained data using IBM SPSS Statistics 20.
Results
We investigated 590 patients, from which 77 men (mean age 54.91 ± 14.902 years old) and 513 women (mean age 52.05 ± 13.635 years old). Our analysis revealed that 10 male patients had thyroid autoimmunity (12.98%) and 155 out of 513 female patients (30.21%, $P = .002$, $r = .129$). The Bethesda based results were: 70 (11.16%) category I, 459 (72.17%) category II, 75 (11.79%) category III, 16 (2.52%) category IV and 15 (2.36%) category V. Autoimmunity was present in 6 cases of Bethesda V (6.66%), 1 case of Bethesda IV (18.75%, 23 cases of Bethesda III (12.5%), 123 cases of Bethesda II (12.66%) and 22 cases of Bethesda I (12.85%), with no statistical significance in neither of these categories, nor comparing malignant – benign or diagnostic – non-diagnostic results. Also, important to mention, the presence of autoimmunity did not interfere with the TI-RADS score, and it was present in only 3 of the 29 cases that were confirmed after surgery as thyroid cancer and in 2 of the 23 patients that were diagnosed with benign thyroid nodules post thyroidectomy (the rest were lost to follow-up).
Conclusions
Considering the lack of information of how the presence of autoimmunity could interfere with the cytological results of nodules referred for FNAB, we tried to demonstrate the the simultaneous diagnostic of thyroid autoimmunity does not tamper with the beneficial outcome of FNAB. Further research is needed in order to assign a more radical conclusion.

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EP421

Screening of thyroid function in pregnant women in Bulgaria

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In Bulgaria there are epidemiological data for the population of 20–80 years for the frequency of thyroid dysfunction – 6.3% hypothyroidism and 3.7% hyperthyroidism (Bulgarian Society of Endocrinology, 2012). So far, there is no national data on the incidence of thyroid disorders in pregnant women, which is a major lack of the health care system and the purpose of this study is to fill this gap.
Material and methods
We studied 547 pregnant Bulgarian women from 10 regions of the country, with mean age 30 ± 5 y. The prevalence of subclinical (SHT), overt (OHT) hypothyroidism, subclinical (SHyperT), overt (OHyperT) hyperthyroidism was determined. TSH, FT4 were measured and ultrasound of thyroid was performed.
Results
Screening find in 20.1% of pregnant women (n-110) SHT, 6.2% (n-34) OHT, 0.9% (n-5) SHyperT and 0.4% (n-2) OHyperT. In 79 (55%) pregnant women hypothyroidism has been known and has been treated – 76 with SHT and 3 – with OHT. There are 65 (45%) pregnant women with newly discovered hypothyroidism – 34 with SHT and 31 with OHT. Thus, of

all 144 pregnant women with hypothyroidism, only 55 (38.2%) under the Levothyroxine treatment achieved an euthyroid state, but the remaining 89 (61%) were hypothyroid (55 with SHT and 34 with OHT), although some were under hormonal treatment. During pregnancy, the proportion of women undergoing treatment with Levothyroxine increased: I trimester – 42%, II trimester – 45%, III trimester – 57%.
Conclusion
The presence of 16.3% of hypothyroid pregnant women (89 of the 547 studied) is a poor certificate for maternal and child health care. In the presence of verbally established risk factors for thyroid disease early diagnosis, timely inclusion of an adequate dose of Levothyroxine and regular monitoring are needed.

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EP422

Ultrasound guided percutaneous laser ablation of thyroid nodules

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Background
Thyroid nodule is the most common endocrine disorder with the prevalence of more than 50% in adults. Majority of nodules are small in size and can be detected only by various imaging methods. Thyroid nodules are usually benign, asymptomatic, and do not need treatment. Growing and large symptomatic thyroid nodules are usually treated with thyroidectomy. Novel minimally invasive ablation techniques can be alternative to surgery. Percutaneous laser ablation is causing irreversible thermal destruction of tissue by conversion of the absorbed laser light into heat. Method is only applicable in benign thyroid nodules.
Aim
To evaluate efficiency and safety of ultrasound (US) guided percutaneous laser ablation of thyroid nodules.
Patients and methods
In our prospective study, we included two male and four female patients with a mean age of 50.5±10.9 years with US isoechoic homogeneous thyroid nodule larger than 3 cm in diameter and 5 ml in volume, which was scintigraphically 'cold' and two times benign on cytology examination (Bethesda 2). Under US guidance optical fiber(s) were inserted percutaneously directly into the nodule through inserter using cranio-caudal approach. In order not to damage surrounding tissue the optical fiber(s) were positioned at least 10–15 mm from nodule border. Depending on nodule volume and size we applied from 1800 J to 8400 J of energy. We used one or two fibers and zero to two 'pull backs'. Outcome was evaluated one week, one month and three months after the procedure. Results are reported as mean±standard deviation. T-test was used for statistical analysis.
Results
Initial mean volume of thyroid nodules was 20.6±7.6 ml (range, 9.4–31.6 ml). Volume of nodules decreased to 14.6±6.6 ml (reduction of 29.1%) at one week, 13.0±5.7 ml (reduction of 36.9%) at one month and 10.8±5.6 ml (reduction of 47.6%) at three months after the procedure ($P=0.0573$, $P=0.0005$, $P=0.0003$, respectively). Regarding adverse effects, one patient reported periprocedural pain in the nodule (VAS score, 3/10), which was not observed after the procedure. In the first week after the procedure two patients reported tension in nodule and headache. No voice changes or other adverse events were observed.
Conclusion
In our initial experience, US guided percutanoues laser ablation of thyroid nodules is effective and safe procedure. Inclusion of a larger group of patients and follow-up for a longer period of time is needed in order to obtain more reliable results regarding efficiency and safety of the procedure.

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EP423

Risk of developing hypothyroidism during pregnancy in women with autoimmune thyroid disease

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Women with positive thyroid autoimmunity are considered at risk of developing hypothyroidism in pregnancy, so monitoring thyroid function is recommended.
Objective
To assess the risk of gestational hypothyroidism in pregnant women with autoimmune thyroid disease and normal thyrotropin (TSH) at the beginning of pregnancy.
Methods
Retrospective review of data from pregnant women attended between April 2016 and October 2019. Women with positive anti peroxidase (anti-TPO) and/or anti thyroglobulin (anti-Tg) antibodies, and normal TSH level in the first trimester (TSH 0.1–4.0 mIU/l) were selected. Thyroid function was monitored throughout pregnancy to assess the development of gestational hypothyroidism, defined as TSH ≥4 mIU/l.
Results
Ninety-nine pregnant women were included, aged 34.2±4.7 years (18–43), 40.4% nulliparous, with mean baseline TSH 1.91±1.05 mIU/l (9th gestational week).
Anti-TPO antibodies were positive in 86.9% of women. All anti-TPO negative women were positive for anti-Tg antibodies. Twelve women were lost during follow-up.
Only 2 women developed hypothyroidism (2%). These women had baseline TSH levels>2.5 mIU/l and reached TSH 4.01 and 4.23 mIU/l respectively in the 15th gestational week, starting treatment with levothyroxine.
Conclusion: In our population, women with positive thyroid autoimmunity and normal TSH levels in the 9th week, appears to have very low risk of developing gestational hypothyroidism. These women would need no additional follow-up during pregnancy.

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EP424

Amiodarone induced thyrotoxicosis

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Background
Amiodarone induced thyrotoxicosis (AIT) is one of the most important and severe complications caused by amiodarone therapy. The multidisciplinary medical cooperation and combined therapeutic strategies are necessary in some cases.
Aim
Analysis of patients suffered from AIT with focus on clinical picture, laboratory findings and possible therapeutic options.
Methods and Results
We performed retrospective analysis of 35 consecutive patients with AIT, (27 men and 8 female, mean age 61.91±9.5 years) who were examined and long-term monitored on Department of Internal Medicine University Hospital Banska Bystrica (Endocrinology section) during the period 2005–2018. All of analysed patients ($n=35$) have been treated for arterial hypertension, 49% ($n=17$) ischaemic heart disease, 63% ($n=22$) had heart failure and 23% ($n=8$) had implantable cardioverter defibrillator. The atrial fibrillation was the most frequent indication for amiodarone therapy (in 71%) and in 29% of patients it was ventricular tachyarrhythmias. The mean time of amiodarone administration was 980±566 days, median 866 days. Mean TSH in the time of diagnosis was 0.024±0.06 mIU/l and mean free T4 was 46.2±16.71 pmol/l. The prevalence of different types of AIT was: AIT type 1 (34%, $n=12$), AIT type 2 (49%, $n=17$) and mixed type AIT (17%, $n=6$). Twenty four patients (69%) had been hospitalized and four patients (11%) developed thyrotoxic crisis. All of patients ($n=35$) have been treated with antithyroid drugs and 13 of them (37%) with corticoids co-administration. The mean time to achieve AIT remission (defined as free T4 decrease to physiological ranges) was 112±52 days, median 99.5 days. In 12 patients (32%) thyroidectomy was performed, in five patients urgently and seven electivly. The thyroid papillary microadenocarcinoma was histologically confirmed in two of observed patients.
Conclusion
Amiodarone induced thyrotoxicosis is one of the most severe complications caused by amiodarone therapy. Thorough knowledge of its adverse effects allow us to perform appropriate therapeutic mesures in care of patients

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EP425

Upregulation of HLA class I and antiviral immune responses in graves' disease

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Background
Graves' disease (GD) is a common autoimmune disease of unknown origin. Evidence of an association between autoimmune thyroid diseases and viral infections is, however, emerging. Human leukocyte antigen (HLA) class I presents both virally and self-derived antigens to circulating immune cells and plays a crucial role in the defense against viral infections. This study aimed to investigate the presence of enterovirus and HLA class I expression in a large GD cohort, with both newly diagnosed and chronic GD patients. In addition, the presence of the coxsackie and adenovirus receptor (CAR) and the viral immune response proteins signal transducer and activation of transcription 1 (STAT1) and protein kinase R (PKR) were examined.
Methods
Thyroid tissue samples from 48 GD patients were obtained from core needle biopsies and thyroid surgery specimens. Thyroid tissue collected from 24 patients during neck surgery for other reasons than thyroid autoimmunity served as controls. Standard immunohistochemistry on formalin-fixed and paraffin-embedded tissue samples were used to detect HLA class I, enteroviral capsid protein 1 (VP1) and CAR. STAT1 and PKR were examined with combined immunofluorescence staining in a subset of the samples.
Results
Significantly more HLA class I positive samples were found in the GD group (25 out of 48 [52.1%]) than in the control group (5 out of 24 [20.8%]) ($P=0.011$). Moreover, the semi-quantitative score (ranging from 0 to 8) assessing the grade of HLA class I expression was significantly higher in the GD group (3.1±3.3) than in the control group (0.5±0.9) ($P<0.001$). VP1 was detected in both controls and GD samples, but with significantly more VP1 positive thyroid cells in the GD samples (50.1±30.5%) than in controls (14.9±10.5%) ($P<0.001$). Nuclear, as well as cytosolic, STAT1 was found in thyroid cells, and was co-localized with HLA class I. In addition, PKR and VP1 were also found co-localized within thyroid cells. Finally, we demonstrate the presence of CAR in thyroid cells.
Conclusion
The current study confirmed that HLA class I upregulation is a defining feature of GD and that enterovirus protein can be found in thyroid tissue. Thyroid cells express CAR, thus confirming a susceptibility to enterovirus infection. The co-localization of HLA class I with STAT1 and VP1 with PKR indicates an intracellular, antiviral host response. These findings support the concept of a firm link between viral infection and autoimmune thyroid diseases.

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EP426

A rare case of isolated central hypothyroidism with thyroxine malabsorption

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Introduction
Hypothyroidism remains a global problem with prevalence of 1–2% in iodine replete areas of the world. Primary or Autoimmune Hypothyroidism remains the most common type of hypothyroidism worldwide. Central (secondary) hypothyroidism (CH) because of pituitary/hypothalamic disorders is a rare cause of hypothyroidism with reported prevalence of 1:20.000 to 1:80.000 in the general population[1]. This makes CH about 1000 fold rarer than primary hypothyroidism. We present an interesting case of a young female who initially presented with biochemical features of autoimmune primary hypothyroidism and subsequently developed isolated central hypothyroidism (ICH) with concomitant Thyroxine malabsorption.
Case report
A 45-year old female patient presented with clinical features of hypothyroidism. Biochemistry showed TSH 5.29 mIU/l & free T4 11.4 pmol/l with strongly positive TPO antibodies (> 1000) suggesting primary autoimmune hypothyroidism. Despite being on increasing doses of Levothyroxine, she remained symptomatic. Serial TFTs showed suppressed value of both TSH & free T4. The results were cross checked by sandwich Delfia assay in a different laboratory which showed consistent pattern of TFTs ruling out assay interference. Further investigations, including full pituitary hormones profile, Short Synacthen Test and MRI pituitary were normal apart from suppressed TSH and low T4 which is indicative of Isolated Central Hypothyroidism. Despite adequate Thyroxine replacement, her free T4 level remained low. Her Coeliac and malabsorption screens were normal. She had supervised Oral Thyroxine absorption test (with 700 mg of Levothyroxine) but subsequent serial measurements of free T4 levels failed to rise above 8.7 pmol/l (Normal range 12–22 pmol/l). As a consequence, patient was offered even higher dose Thyroxine replacement and planned for trial of intravenous thyroxine but she chose to move her care to a different hospital.
Discussion
This is a very rare case of primary hypothyroidism which later transformed into central hypothyroidism of unknown aetiology and also developed Thyroxine malabsorption. If relied solely on the TSH level, the primary care practitioners can be caught out by the persistently low TSH being perceived as Thyroxine over replacement and potentially inadvertently reducing the Thyroxine dose and delay in diagnosis of central hypothyroidism. This leads to a question whether T4 should be routinely tested even for diagnosis and monitoring of all patients with suspected hypothyroidism.
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EP427

Thyroid function in pregnancy and atmospheric pollution

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Introduction
Exposure to air pollution and in particular to nitrogen dioxide (NO_2) or particulate pollutants less than 2.5 μm (PM2.5) or 10 μm (PM10) in diameter has been linked to thyroid (dys)function in pregnant women. The environmental degradation that has occurred in recent years in the region of Athens led us to a local study of air pollution against thyroid function in pregnant women in Athens. We hypothesized that there may be a dose-effect relationship between air pollutants and thyroid function parameters.
Methods
We retrospectively evaluated thyroid function with thyrotropin (TSH) in 293 women, mean±S.D.: 30.9±5.5 years, vs the mean of the previous 9 months of NO_2, PM2.5 and PM10 levels of five atmospheric air quality measurement stations in the greater Athens area (2013–2017). All the women had no prior thyroid disease and were diagnosed with hypothyroidism for the first time during their pregnancy (mean±S.D. gestational age at diagnosis 19.4±8.6 weeks, weight gain 5.1±5.6 kg, TSH: 4.54±1.66 mIU/l). We only included women with TSH>2.5 mIU/l or>3.0 mIU/l if the initial thyroid assessment was done in the first or the second trimester of pregnancy respectively. Exposure to air pollution for each woman was considered according to her place of residence (permanent residence for at least one year) within a reasonable distance of one of the five air quality measuring stations. Statistical analysis of age, pregnancy weight change, and air pollutants vs TSH was performed with ordinary least squares regression (OLS-R) and quantile regression (Q-R).
Results
Using OLS-R, a significant (positive) correlation for logTSH was found only with PM2.5 ($r=+0.13$, $P=0.02$). Analysis with Q-R showed that each incremental unit increase (for the 10th to the 90th response quantile) in PM2.5 increased TSH (± S.E.) between+0.029 (0.001) to+0.025 (0.001) mIU/l ($P<0.01$). Other pollutants (PM10 and NO_2) had no significant effect on TSH.

Conclusion
Our results indeed show a relationship between PM2.5 and TSH. The mechanisms involved in the pathophysiological effects of atmospheric pollutants, in particular PM2.5, are being investigated.

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EP428

The hypothyroid adrenals, transient thyro – adrenal failure – functional or real?

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Background
Primary hypothyroidism is one of the most common endocrine disorder, prevalence is in the ranges of 3.8–10.9%. It has been estimated that about 42 million people in India suffer from thyroid diseases. At one end,with easier availability of the assays and better affordability we are now able to diagnose and treat hypothyroidism much earlier. At the other end, we are seeing patients with TSH > 100 at diagnosis, most of them done as a part of routine screening often with no other comorbidities.
Materials and methods
The present case series is a descriptive and observational case control study of 25 consecutive cases diagnosed on routine screening with TSH > 100. We assessed the Zulweski clinical score, BMI, goitre grading as a part of the clinical examination. Biochemical evaluation included an 8 AM cortisol, prolactin and T_3, T_4 TSH. LT_4 replacement was started in all.
Results
The median age of presentation was 26.76 years and 96% were women. Weight gain was a presenting feature only in less than one third of the cases. The commonest feature of presentation was easy fatigability. Prolactin was elevated in 64% of the cases. 0800 h cortisol levels were normal in two-thirds of the cases. Three (12%) cases presented within 72 hrs of taking LT_4 with fatigue, tiredness, headache and hypotension (all had low cortisol). They were managed with intravenous followed by oral hydrocortisone. On follow up, we could withdraw Hydrocortisone within a period of three months.
Conclusion
In this series severe primary hypothyroidism was not associated with weight gain in most. Twelve percent of the cases had clinical and biochemical hypoadrenalism after levothyroxine therapy. Routine replacement with steroid is not indicated in all cases of severe hypothyroidism but when dealing with severe primary hypothyroidism as in our cases, a check on Cortisol is worth considering along with a careful watch for the clinical symptoms of hypoadrenalism in the first few days after starting levothyroxine treatment. Baseline 8 AM cortisol may help in predicting the precipitation of adrenal failure post levothyroxine.
Keywords: hypothyroidism, thyro-adrenal failure, lazy adrenals.

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EP429

An audit of monitoring of fetus in pregnant women with hyperthyroidism

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Aim
Hyperthyroidism can affect pregnancy outcomes based on activity of the disease, ongoing use of anti-thyroid drugs (ATD) and TSH receptor antibody (TRAB) positivity. The aim of our audit was to analyse the outcomes of fetal monitoring in pregnant women with previous or current history of active hyperthyroidism
Methods
The data on all patients with hyperthyroidism and pregnancy over 3 years was collected. The local guidelines recommend TRAB check at 20 weeks. If TRAB + and/or patient continuing on ATD into third trimester, fetal medicine scan(FM Scan), serial growth scans in third trimester and a neonatal alert for a new-born review were arranged.
Results
N = 56. This included women with active Graves' (*n* = 34); previous hyperthyroidism currently in remission (*n* = 15) and post radio-iodine or thyroidectomy induced hypothyroidism(*n* = 7). Of the Graves' patient, 19 required ATD continuing into 3rd trimester, with the rest withdrawing ATD during the course of early pregnancy
TRAB ±
N = 31; FM Scan normal in 30 patients-1 patient had an abnormal scan (hydronephrosis) which was likely unrelated to the thyroid disease. Serial growth scans were done in 26/31 women– 20 normal; 3 had large for gestational age (1 on thyroxine, 2 were euthyroid on no ATD) – one had normal birth weight, one was born preterm at 30 weeks, other baby was 3.7 kg at birth. 3 had small for gestational age (1 on thyroxine, 2 were euthyroid on no ATD)- one had twin pregnancy, one had pre-eclampsia with known hypertension and the third baby was well after delivery. On looking at the women who did not have growth scans (due to recent change in local guidelines), 4 had only weakly + TRAB and 1 had premature rupture of membranes attributed to likely placental issues.
Patients on ATD
N = 19; FM Scan was normal in all 19 women and were normal. Serial growth scans (*n* = 18) were normal in 16/18 women-2 had small for gestational age which is not consistent with ATD use and both had normal TFT. (1 patient who did not have the growth scan was the patient with premature rupture of membranes).
Conclusion
The study shows generally good outcomes for patients with hyperthyroidism. Serial growth scans can be used as a preliminary screening to guide further monitoring during pregnancy to monitor for TRAB or ATD or active Graves' related impact to pregnancy. Fetal medicine scans may be reserved for patients with high TRAB as they have generally been normal.

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EP430

Antithyroperoxydase autoantibody evolution in Hashimoto thyroiditis. Comparison between all re-evaluated patients and those over 10 years observation. January 2020

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Aim
Most research teams analyze the evolution of patients with Hashimoto thyroiditis (HT) on syndromic basis (e.g., the thyroid function), not on pathogenic basis (the autoantibodies). Thus, most researchers refer to thyroid hormone evolution. In this study we re-analyzed (first in 2018) how evolve the antithyroid autoantibodies. Therefore, we analyzed the antithyroperoxydase antibodies (ATPO) evolutive patterns in patients with HT.
Method
1. ATPO levels were analyzed in several accredited Bucharest laboratories. 2. Only patients with minimum 3 investigations were considered for interpretation. 3. We considered 5 ATPO evolutive patterns: a. undulatorious; b. decreasing; c. increasing; d. unmodified, e. normalization. 4. Unmodified pattern was considered if ATPO level did not differed by 5%. 5. normalization pattern was considered if ATPO decreased under the *cut off* level (= 34 IU/ml).
Results.
A. All Patients: 893; women – 831, men –62 (7.46%).
B. Patients re-evaluated over 10 years: 97; woman: 89; men: 8 (8.99%).
C. The reinvestigation final time for all patients: average: 4.28 years; median: 3; minimum: 2 months, maximum: 24.5 years.
D. For patients with over 10 years observation; average: 12.56 years; median: 12; minimum: 10 years, maximum: 24.5 years
E. ATPO level at onset (at diagnostic time) for all patients re-analyzed: average: 789.55 IU/ml, standard deviation: 2129.
F. For patients observed over 10 years: average; 607.86 IU/ml, S.D.: 941.
G. The evolution patterns for all patients: a. undulatorious – 425 patients (47.59%); 12 without thyroid (3 = TXT/total thyroidectomy, 3 = 131-I, 6 = atrophy); b. decreasing but with ATPO over the *cut off* limit – 233 (26.09%); 6 without thyroid (3 = atrophy, 2 = TXT, 131-I = 1); c. increasing: 156 (17.47%); 1 = TXT; d. unmodified: 58 (6.49%), 2 no thyroid (1 = 131-I, 1 = TXT); e. normalization: 21 patients (2.35%), 5 no thyroid (2 = atrophy, 3 = TXT).

H. ATPO patterns in patients seen after 10 years observation: a. undulatorious: 76 (78.35%), vs all, $P << 0.001$; b. decreasing: 14 (14.43%), vs all, $P << 0.001$; increasing: 1 (1.03%); unmodified: 1 (1.03%); e. normalization: 5 (5.15%).
Conclusions
1. When performed more ATPO analysis (over 10 years), the evolutive pattern become undulatorious, around 80% patients. 2. When thyroid is missing, ATPO decreased level were registered till normalization.

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EP431

Treatment of benign thyroid nodules in Spain with HIFU. Importance of its size, situation and painful sensation in the results. 18 month follow-up

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Objectives
Assess the response of benign thyroid nodules to HIFU treatment depending on their volume and localization. Know if the treatment is painful when sedation is not used.
Methods
66 patients with benign thyroid nodules (Bethesda Category II) were treated with HIFU (Echopulse Theraclion). They were grouped in 3 categories by maximal nodule diameter as assessed by echography. Group 1: nodule diameter between 14 and 20 mm; Group 2: between 21 and 30 mm; Group 3: over 30 mm. Follow-up at 8 weeks, 6, 12 and 18 months was done under echography. Nodules are described as superficial or deep taking the center line of the trachea as a reference. We define therapeutic success when the nodule size, after 8 weeks of the last treatment, is inferior to 50% of its initial size. All patients followed the same pre-treatment oral analgesia protocol: Lorazepam 1 mg+Paracetamol 1.000 mg+Dexketoprofene 25 mg. Assessment was made using a categorical 6-grade scale (CS).
Results
Results from groups 1 and 2 are significantly different from those from Group 3. 81% of Group 1 cases reach therapeutic success with a single treatment. Groups 2 and 3, have respectively 58% and 42% of success. In cases from Groups 2 and 3 treatment is repeated up to 4 times. Deeper nodules and nodules located on the isthmus can only be treated partially. There has been no recurrence or enlargement of treated nodules after 18 months. Patients describe pain as 'tolerable' in 68% of cases. In 23% of cases pain is marked as 'almost intolerable', which needed to lower the delivered power by 5–10 W. Lastly, in 9% of cases pain was marked as 'intolerable' leading the treatment to finalize without being totally performed. Pain sensitivity is less and less tolerated for Group 3 nodules of longer treatment durations, as oral analgesia efficacy decreases in time.
Conclusions
The treatment of benign thyroid nodules with HIFU is safe and effective. The size of thyroid nodules is an important factor to design of the treatment strategy with HIFU. Nodules under 30 mm diameter are the best choice in terms of treatment speed, efficacy and obtained results. For bigger nodules, several sessions and a follow-up over 18 months are necessary to obtain satisfactory results. Deeper nodules and nodules located on the isthmus need a previous simulation treatment to assess the expected reduction. Our protocol for oral analgesia is successful for nodules that do not require long treatment times, and on patients that feel relaxed and have a better self-control management.

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EP432

Clinical approach after a Bethesda 4 result in a thyroid cytology

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Introduction
Thyroid nodules are a very common finding in sonographies (20–75% people). Criteria for clinical management and for cytological diagnosis (Bethesda system) are well standardized. In spite of this, a gap of knowledge exists as far as management of Bethesda 4 is concerned.
Aim
Evaluate the clinical approach of Bethesda 4 (B4) result in a thyroid cytology.
Material and methods
Retrospective study of thyroid nodules classified as B4 in FNA in our hospital between 2012 and 2018. Statistical analysis: SPSS v.22.0 (Student' t-test to compare means and
Squared Chi/Fisher to proportions).
Results
162 nodules classified as B4 in FNA. Mean age: 54.07±14.62 years. 75.3% Women. 138 (85.2%) were surgically removed: 11.6% of them were part of a multinodular goitre; 55.8% follicular adenomas; 10.9% follicular carcinomas; 8.7% papillary carcinomas; 1.4% medullary carcinomas; 11.6% NIFTPs. In 24 cases there were not a surgical treatment: In 12 of them active surveillance was decided in accordance to patients' preferences, in 10 of them surgical treatment was put off because of an intercurrent neoplasia and 1 patient died of an unrelated cause.
Conclusions
In our cohort, proportion of B4 thyroid nodules and carcinoma result after surgery doesn't differ from previously published results. Although the use of this category seems correct, it gives rise to a surgical overtreatment in hyperplasic nodules.

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EP433

The effectiveness of the thyroid disease screening program in pregnant women in the slovak republic 2016 compared to 2011

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Objectives
Thyroid screening in pregnancy has in Slovakia started in 2009 on the basis of a ministerial guidance for diagnosis and therapy of autoimmune diseases of thyroid gland in pregnant women. (source: Vestník MZ SR 39., 2009, pp. 33–39). Its effectiveness was analysed in 2016 and compared with a similar analysis from 2011. The analysis was aimed to verify the implementation rate of the Guidance in practice.
Methods
Records from pregnant women registered in the Health Insurance Company Dôvera (28% share in Slovakia) were evaluated. Included were women with documented first visit at gynecologist who confirmed pregnancy in 2016. Examination of blood sample for TSH and APTO followed by examination by endocrinologist with negative anamnesis of appointments with endocrinologists in 2015 were including criteria for the analysis. All women were monitored till the end of 2017.
Results
16 891 women were included. Out of them 5 901 (34.9%) underwent a „mandatory 'examination for TSH and ATPO. Out of these 526 (i.e. 8.9% of 5 901) were subsequently examined and followed up by endocrinologist also in 2017 for thyroid pathology of TSH and/or ATPO. 210 women (39.9% of 526) in the latter group needed medicament treatment: 6 women (2.9%) for hyperfunction and 204 women (97.1%) for hypofunction of thyroid gland with average daily dose 74.5 mg thyroxin. Thyroid disease screening in pregnant women implemented by gynecologists in 2016 was low reaching 34.9%, however, surprisingly it was even lower than in 2011 when it reached 37.1%. Newly diagnosed thyreopathy reached only 3.1% in the whole group of 16 891 women, and thyreopathy with needed treatment only 1.2%. The overall screening costs amounted to 135 922 €, i.e. 23€ per one woman. Average costs of one identified thyreopathy were 258.4 € and of one treated thyreopathy 647.3 €.
Conclusions
The high proportion of laboratory thyreopathies in 2016 requiring long-term follow up by endocrinologist (8.9% in the group with examined TSH and ATPO) and necessity of a long-term therapy in this group (39.9%) allow to conclude that this screening is clinically as well as cost effective and should be performed on the whole population of pregnant women. The Low implementation of the screening by out-patient gynecologists despite the ministerial guidance has been in force for seven years is a critical weakness.

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EP434

Alteration in thyroid function in a sample of Egyptian female patients with breast cancer receiving adjuvant chemotherapy

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Introduction
Chemotherapy, as a systemic therapy, is one of the most effective modalities for cancer treatment. However, the use of chemotherapeutic drugs in patients with breast cancer can lead to thyroid dysfunction. The aim of our work is to determine the influence of adjuvant chemotherapy on thyroid function in female patients with breast cancer after radical mastectomy and before radiotherapy.
Materials and methods
Our study was conducted on 40 Egyptian female patients(18–60) years of age who received adjuvant chemotherapy with 5-flourouracil, epirubicin and cyclophosphamide for breast cancer after mastectomy and before radiotherapy. Free T3, Free T4, TSH, anti-thyroglobulin antibody and thyroid peroxidase antibody were measured before treatment and after the 6th cycle (six months) of chemotherapy.
Results
On comparing the results of the studied group before and after chemotherapy, there were high significant difference in TSH value $P=0.005$ being higher after chemotherapy (2.42 mU/l before chemotherapy vs. 2.87 mU/l after chemotherapy), significant difference in free T4 values $P=0.025$ being lower after chemotherapy(1.32 ng/dl before chemotherapy vs. 1.23 ng/dl after chemotherapy), but there was no significant difference in free T3 value $P=0.051$, Concerning both anti-thyroglobulin and anti-peroxidase there was no change in values before and after chemotherapy.
Conclusion
Receiving adjuvant chemotherapy in breast cancer patients was associated with significant elevation of TSH and decrease in fT4 levels which in spite of still being in the normal range, it may lead to overt hypothyroidism with longer duration of follow up.

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EP435

Significance of serum thyroglobulin levels in differentiated thyroid carcinoma patients with distant metastasis

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Background
Distant metastases develop in approximately 5–10% of patients with differentiated thyroid cancer (DTC). Nearly 70% of this subset will become radioiodine refractory (RAI-R) with a poor prognosis. Recently, the multikinase inhibitors (MKIs) showed promising results of treating these patients. It has become crucial to identify RAI-R DTC early. This study was conducted to identify the predictors of RAI-R disease in patients with distant metastasis secondary to differentiated thyroid carcinoma (DTC).
Methods
A retrospective review of 1665 patients with DTC treated at a regional tertiary hospital in Kaohsiung, Taiwan between 1986 and 2010 was performed. Medical records relating to a total of 207 patients with pathologically verified DTC were studied, and all of whom were found to have distant metastasis at diagnosis or during follow-up. Predictor analysis included age, sex, histology, cancer stage, site of metastatic foci, thyroglobulin (Tg) level and accumulated therapeutic dose of radioiodine (RAI). Cases with positive anti-Tg antibody were excluded from analysis.
Results
Approximate 80% of this cohort had papillary carcinoma or its variants whereas others reported follicular carcinoma. The mean age at diagnosis of distant metastasis was 46 years. The female to male ratio was 2:1. The independent predictors of radioiodine refractory disease were old age (> 55 yr) and high TSH-stimulated Tg level (> 400 mg/l) at the discovery of metastasis.
Conclusion
High level of TSH-stimulated serum Tg levels can be used as a indicator in DTC patients with distant metastasis to predict RAI-R disease. Old age is also a risk factor of RAI-R disease.

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EP436

Coexistent thyroid and lung cancers resembling flip flop phenomenon

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Introduction
Differentiated thyroid cancer (DTC) prognosis is usually favorable, even when metastatic radioiodine avid disease is present. Radioiodine-refractory disease, usually a sign of higher aggressiveness, can be detected by ^{18}F-FDG-PET/CT. There is a reverse relationship between iodine and FDG accumulation in thyroid cancer lesions, the so-called ''flip-flop'' phenomenon: when thyroid cancer cells dedifferentiate they tend to lose their radioiodine avidity and start uptaking FDG. We present a case of advanced DTC with heterogeneous uptake of iodine and FDG.
Case presentation
A 69 years-old woman with a past history of right hemithyroidectomy 8 years before, due to a 70 mm hyperplastic nodule, was referred to our center. The patient had a painful lesion in the right acromion whose biopsy suggested papillary thyroid cancer (PTC) metastasis. Histological review of slides of the previous right thyroidectomy revealed PTC (encapsulated follicular variant) with vascular invasion. Neck ultrasound from the remaining thyroid showed irrelevant findings. However, CT scan documented extensive metastatic disease in the upper mediastinum, lungs with micronodules and a large lesion with 49 mm in the left lower lobe, chest wall and right acromion. The patient was submitted to radiotherapy (20Gy) with improvement of the shoulder pain. The histological piece of the remaining thyroidectomy revealed no neoplastic lesions. Then, she was submitted to radioiodine therapy with 150 mCi. Stimulated thyroglobulin was > 300000 ng/ml and the whole-body scintigraphy revealed metastatic disease in the right shoulder, chest wall, pelvis and left femur but no uptake in the lungs and mediastinum. ^{18}F-FDG-PET/CT was performed and revealed several lesions with elevated metabolism in the mediastinum, pulmonary left hilum and lower left lobe with 61 mm (SUV 22) and contralateral lung, while the lesions referred in the previous 131 I scintigraphy only showed a slight to moderate metabolism (maximum SUV of 7). Due to ^{18}F-FDG uptake discrepancy within the lungs, the larger left lobe and mediastinic lesions were biopsied by bronchoscopy; the immunohistochemistry was negative for thyroglobulin and PAX 8 and positive for TTF1, suggesting lung adenocarcinoma. The patient was referred to a second radioiodine therapy with 150 mCi and also for lung-directed chemotherapy.
Conclusion
In the presence of flip flop phenomenon, a well-described characteristic of progessive DTC, a high suspicion index must be maintained when the findings are discordant, in order to provide an appropriate differential diagnosis and management of the disease.

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EP437

The learning curve of a new thyroid fine-needle aspiration facility

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Fine-needle aspiration (FNA) is the best available technique for preoperative diagnosis of malignancy in thyroid nodules. Although its efficiency has been well described, the learning curve is underreported. We aimed to describe the learning curve of a new FNA facility (endocrinologist/pathologist) in a university based hospital.
Methods
In February 2018 a new FNA facility was formed in our hospital comprising an endocrinologist with high experience in thyroid ultrasound but without any experience in FNA and a pathologist with occasional activity in thyroid FNA. We assessed all FNA procedures of thyroid nodules until December 2019 (791 nodules). The nodules were chronologically grouped in 4 groups of 200 nodules (191 in the last group).
Results
The number of slides per nodule decreased from 5 ± 1.6 in the first group to 4.9 ± 1.4, 4.3 ± 1.0 and 4.1 ± 1.1 in the second, third and fourth group respectively (ANOVA $P<0.001$) while the nodule greatest dimension remained constant (around 26 mm). The percent of Bethesda 1, 3 and 4 decreased

from 14.5%, 12.5% and 31.5% in the first group to 10.5%, 10% and 18.5% in the second, 5%, 5.5% and 9.5% in the third and 10.5%, 3.7% and 10.5% in the last group. In surgically treated nodules the risk of malignancy 100%, 100%, 92.3% and 100% respectively for Bethesda 5/6 and 30.6%, 36.3%, 22.2% and 60% respectively for Bethesda 4 categories.
Conclusion
The efficiency parameters of a new thyroid FNA facility continue to improve at least until 800 procedures. However, most parameters are within the literature reported range after 200–400 procedures.

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EP438

Determination of daily iodine consumption amount of people with nodular goitre and relationship with papillary thyroid cancer

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Objective
There is a risk of malignancy in 5–10 percent of all thyroid nodules. The most common type of thyroid cancer is papillary thyroid cancer (PTC).There are some risk factors has been found in differentiated thyroid cancers like high iodine intake. However, in people with severe or moderate iodine nutritional deficiency (<75 μg/day),an increased risk of thyroid cancer was found 2.6 times higher than those with optimal iodine nutrition (150–299 μg/day) in a research. In another one, PTC was found related relatively low or excessive iodine intakes in an adequate area of iodine. In our study we aimed to find daily iodine consumption amounts in patients with nodular goitre (NG) and PTC. We searched the frequency of consumption of iodine-rich foods and goitrogen foods. Anthropometric measurements, some blood values and the properties of nodules on ultrasonography were also investigated and compared the in these two groups.
Material and method
The study was designed on the basis of patients with 64 benign NG group and 50 malignant PTC group according to the result of the fine needle aspiration biopsy (FNAB) of the thyroid nodules whose applied to Endocrinology Outpatient Clinic of a private medical center in Istanbul between October 2015 and November 2019. The data of the research taken by demographic and daily food consumption questionnaire (FFQ). Daily consumption of iodine from the FFQ questionnaire calculated with the Nutrition Information System (BEBIS-BESLENME BİLGİ SİSTEMİ) version 8.2 developed for Turkey. Iodized salt amount using with meals calculated from demographic questionnaire has also been added the total iodine consumption in the survey. Results are evaluated according to WHO criteria. TSH, TPOAb, TgAb, fasting glucose, insulin, total cholesterol, LDL cholesterol were examined in the participants. In addition, the number and properties of nodules were examined with ultrasonography and anthropometric measurements were taken
Results
At the end of the study, daily iodine consumption in the PTC group were significantly higher than the benign group. TSH, TgAb and TPOAb were higher in PTC groups, while total cholesterol and HDL cholesterol were significantly higher in the benign group. The foods like shellfish, eggs and cheese, rich in iodine, are consumed significantly more in the benign group. In conclusion, we can say that excess iodine taken is associated with papillary thyroid cancer,but not with iodine-rich food consumption. However large number case studies would give us to chance reveal more precise results about the potential relationship PTC with higher iodine intakes.

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EP439

Next generation sequencing of 12 gene panel in differentiated thyroid cancer

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Introduction
Next-generation sequencing (NGS) in thyroid cancer allows for high-throughput sequencing analysis of various genetic alterations and provides a useful information of tumor biology. NGS Studies on follicular differentiated thyroid cancer have been scanty from Indian subcontinent. In this context, we set out study the prevalence of a genetic panel wide somatic mutations in thyroid cancer.
Material and methods
This prospective study was conducted on 40 paraffin embedded thyroidectomy surgical tissue samples. Institutional ethical committee approval was obtained. Followup details are documented and analysed. Mutation analysis with a 12-gene mutation panel using real-time PCR and ThyroSeq v2 on the Ion Torrent PGM sequencer was employed.
Results
Common single nucleotide polymorphisms (SNPs) with a minor allele frequency of >0.05, as documented in dbSNP; noncoding region variants; and variants in repetitive regions were excluded. Mutations were also manually checked using the Integrated Genomics Viewer v2.4.10 to filter out false positives. The analysis found mutations commonly in BRAF (30)), CDKN2A (19), NRAS (12), PI3KCA (17), RET (8), RAS (24) and TP53 (5) genes. The common mutations found in the samples was RET (M918T), NRAS (Q61R), BRAF (V600E) and missense mutation in TP53(c.217 – c.1178). A mutation has also been identified in KMT2D gene in two of the patient samples. BRAF, CDKN2A, PI3KCA were more common in papillary cancer; RAS, NRAS, RET mutations were common in follicular cancer; TP53 and KMT2D were seen only in poorly differentiated cancer.
Conclusions
NGS helps in patient management, providing risk stratification and subtyping of malignancy. It can be used in molecular tumor classification, and molecular prediction of recurrence and metastasis in thyroid carcinoma. To the best of our knowledge, this is one of its kind study from Indian subcontinent
Keywords: thyroid cancer, BRAF gene, RAS gene, genomics, mutation

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EP440

The relationship between clinicopathological factors and recurrence risk of papillary thyroid cancer

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Introduction
Papillary thyroid carcinoma (PTC) is the most common type of differentiated thyroid cancer, accounting for about 80% of all cases of thyroid cancer. 20 – year survival rate is about 90%. However, PTC can be aggressive – up to 30% of the patients have local renewal or systemic spread.
Our objective was to evaluated the clinicopathological factors of recurrence in completely resected PTC patients.
Methods
A retrospective review of a prospectively maintained thyroid cancer database was performed. Study included 102 patients with histopathologic diagnosis of PTC, treated at Hospital of Lithuanian University of Health Sciences, Kaunas clinics between 2004 and 2017. Patients were divided into: remission group – patients who had no recurrences for at least 1 year after total thyroidectomy and postoperative I^{131} therapy; recurrence group – patients who had local or systemic tumour recurrences for at least 1 year after total thyroidectomy and postoperative I^{131} therapy. Multivariate analyses were performed to identify predictive factors of PTC recurrence patterns. Descriptive statistics was performed, Student´s t test or Mann-Whitney U test for independent samples, Chi-Square for qualitative data.
Results
Study included 51 patients in each group. Average age at diagnosis was 63.51±6.47 years in remission and 53.16±15.6 years in recurrence group ($P<0.001$). The higher rate of recurrence was statistically significant among younger than 55 years old patients ($P<0.001$). There was no significant difference between gender, multifocality, Hashimoto' thyroiditis and rate of PTC recurrence ($P>0.05$). Most common histologic type of recurrence was

classic PTC 80.5% ($n=33$) ($P<0.001$). Classic PTC histology was associated with greater incidence of AJCC tumour stage and lymph node metastasis ($P<0.001$).
Conclusion
This analysis included comparison of the associations between clinicopathologic factors, histological sub-types and recurrences of PTC. We found evidence that younger age and classic PTC sub-type is associated with increased recurrence rate of PTC. Our study lend support to recent data indicating that classic PTC confers a worse prognosis. But further studies are also warranted to expand upon our findings.

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EP441

Management difficulties in nodular goiter associated with hypopharynx infiltration – case report

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Introduction
The connection between the pharynx and thyroid is close, so in the situations of concomitance: thyroid nodules and pharynx infiltration is very difficult to establish the primary lesion. Extralaryngeal spread of laryngopharyngeal cancer to the thyroid gland can occur by three pathways: direct extension, lymphatic spread or hematogenous spread. Of these three mechanisms, direct extension is the main mechanism because of the close anatomical relationship of the thyroid gland to the laryngopharyngeal region. In the same way the thyroid cancer spread to laryngopharyngeal region also mainly by direct infiltration of the tumor.
Aim
To present a rare case of hypopharyngeal cancer (typical for men aged 55–70 years with a history of tobacco use and/or alcohol ingestion) in a relative young female patient with nodular goiter as first symptom.
Case report
A 48 years old woman with dysphagia and throat pain for past 4 months presented at clinical examination a large goiter (nodules over 2 cm in size in both lobes). Neck ultrasound outlines two round thyroid nodule (one for each lobe) situated in the superior poles close to the thyroid capsule: ACR TI-RADS score 5 points. The indirect laryngoscopy described total left and partial right vocal cord paralysis and computer tomography investigation revealed massive hypopharynx infiltration. Due to the ACR TI-RADS score, a fine needle aspiration biopsy from both thyroid nodules was performed and the histological result displayed only squamous cells with no thyreocites. Hypopharynx biopsy confirmed squamous cell carcinoma and the patient underwent tracheostomy and enteral feeding due to the important and rapid local obstruction. In addition she underwent palliative radiotherapy and chemotherapy.
Conclusion
Thyroid gland involvement is not common in hypopharyngeal squamous cell carcinoma. Cases that involved the post-cricoid area, subglottic extension, extralaryngeal spread are associated with a higher risk of thyroid gland invasion. The particularity of our case consist in the presence of hypopharyngeal cancer in a relativ young female alredy with local metastases in the thyroid gland. Besides the two options: thyroid cancer with hypopharyngeal infiltration or hypopharyngeal carcinoma with thyroid metastasis a third hypothesis would have been plausible: papillary thyroid cancer coexisting with squamous cell carcinoma of the upper aerodigestive tract.

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EP442

Anaplastic thyroid carcinoma: About 6 cases

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Introduction
Anaplastic thyroid carcinoma also known as undifferentiated carcinoma is a rare and highly aggressive malignant tumor. It continues to rank as one of the deadliest diseases worldwide and carries a very poor prognosis. It is an aggressive locoregional disease with a high metastatic capacity. There is no agreement with regards to the best treatment.
Material and methods
We reporteded 6 cases of anaplastic thyroid carcinomas treated in the ENT department of Tahar Sfar Hospital in Mahdia. Clinical manifestations and treatments were analysed during a period of 26 years (1996–2018).
Results
The median age was 65 ranging from 47 years to 78 years. Females were more affected, 5 cases occurred in women and one male. The common manifestation was neck enlargement which is associated to hoarseness in two cases. Duration before diagnosis ranged from 4 weeks to 20 weeks with an average of 14 weeks. ALL the cases had lymph node metastases, 4 cases had trachea invasion, 4 cases had subhyoid muscle invasion. One patient had bone metastasis. Histological findings were consistent with the diagnosis of anaplastic carcinoma. Histological examination was performed in total thyroidectomy specimens in 2 cases, and in a microbiopsy of the thyroid gland in 4 cases. A tracheostomy was performed for 3 cases. Four patients underwent total thyroidectomy and 2 patients had inoperable cancer. All patients received Radiation Therapy. All the *patients died within* the follow-up period of 11 months (ranged from 8 to 13 months).
Conclusion
Complete surgical resection is associated with better survival but is very difficult to achieve due to aggressive biological behaviour. Multimodal therapy is associated with better survival and a better quality of life. There is a need for more effective systemic treatments as extensive surgical resections have little overall benefit in highly invasive and metastatic disease.

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EP443

Medullary thyroid cancer, papillary thyroid microcarcinoma and Sarcoidosis: a curious association

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Introduction
Medullary thyroid carcinoma (MTC) represents 3–10% of all thyroid cancer. The presence of papillary thyroid microcarcinoma (mPTC) in patients undergoing thyroidectomy for multinodular goiter has been reported as 3–7%. The occurrence of multiple thyroid cancers of different origin in one individual patient is a rare event. We report the case of synchronous papillary and medullary thyroid cancer developed in heterogynous recurrent goiter of a patient with sarcoidosis.
Observation
A 68-year-old female patient was followed up in our endocrinology department for a heterogynous recurrent goiter for 7 years. The biggest nodule measured 10 mm and was assessed as EU-TIRADS 3. She reported a history of a thyroid nodule(s) operation 2 decades ago and a cutaneous and pulmonary sarcoidosis 5 years ago. Due to a recent size increase of the left thyroid nodule, becoming in EU-TIRADS 4 class, a fine needle aspiration (FNA) and plasma calcitonin (PC) were indicated. Although the cytology exam was benin, high PC levels were noted (266 and 803 ng/l). A second FBA classified the nodule as Bethesda 4. MTC was highly suspected as calcitonin in FNA biopsy and plasma carcinoembryonic antigen (CEA) were elevated (2000 ng/l and ng/ml, respectively). We could not find any sign of an accompanying multiple endocrine neoplasia syndromes and the metastatic work-up was negative. A total thyroidectomy and bilateral mediastino-recurrent lymph node dissection were performed. The anatomopathological study disclosed a MTC and a mPTC. The PC and CEA were normal postoperatively.
Conclusion
The particularity of our case are, besides the simultaneous coexistence of 2 types of thyroid cancer, their slow evolution and their nonmetastatic invasion. The carcinogenic transformation can be due to a potential neoplastic sarcoidosis effect. Further investigations are needed in order to understand and validate the pathogenetic link between sarcoidosis and thyroid neoplasia.

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EP444

Can platelet and neutrophil to lymphocyte ratios be used as predictive markers for malignancy in thyroidectomy patients?

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Objectives
In recent studies, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are being investigated as prognostic and diagnostic markers for many malignancies, including thyroid cancer. The aim of our study was to investigate if a relationship exists between NLR and PLR and thyroid cancer.
Materials and methods
We retrospectively analysed the files of 953 patients who underwent thyroidectomy in our surgery department between January 2012 – December 2017. In the study were included 205 patients with differentiated thyroid carcinoma (DTC) and 108 age- and gender-matched patients with benign thyroid pathology. Anthropometric, biologic and imagistic data, indication of thyroid surgery, surgical procedures and pathology results were recorded.
Results
Age at diagnosis was 52.06±13.22 years for DTC patients (83.4% women) and 52.07±12.902 years for patients with benign thyroid pathology (83.3% women). Before surgery, NLR and PLR were similar in both groups (2.40±1.03 in the DTC patients vs 2.41±1.38 in benign pathology patients, $P=0.958$, respectively 137.6±47.29 vs 130.69±44.22, $P=0.209$). Younger DTC patients had significantly higher PLR than those with benign pathology (under 45 years: 145.79±49.67 vs 45 years and older: 116.50±34.26, $P=0.006$; under 55 years: 142±47.97 vs 55 years and older: 125.30±42.26, $P=0.030$). In the DTC group, men had significantly higher NLR compared to women (2.75±1.10 vs 2.33±1, $P=0.029$). Post surgery, NLR was 2.65±1.37 vs 2.17±0.89 ($P=0.063$), while PLR was significantly higher in the DTC group than in the benign pathology group (147.96±54.47 vs 125.05±34.95, $P=0.025$).
Conclusions
In our study, men with DTC had higher NLR than women, while PLR was higher in the cancer group, but statistical significance was obtained only for younger patients (< 45 and<55 years) before surgery and after surgery for all DTC patients compared to benign pathology group. This could be explained by the changes in immunity that appear with aging, but the relationship between NLR and PLR and thyroid cancer needs to be further investigated.

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EP445

Clustering techniques for thyroid nodules malignancy inference in the era of personalized medicine

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Introduction
Thyroid nodules (TN) are common entities usually discovered during a physical exam or by chance with ultrasound (US) procedures performed for reasons different from thyroid check. The majority of nodules are benign, notwithstanding the growing incidence of thyroid cancer (TC), which increases much largely as compared to all other tumours each year and will be, presumably, the most incident malignancy in women after breast cancer. The clinical challenge relies on the accurate identification of malignant nodules needing attention since the very beginning of the diagnostic process from nodules that will follow an indolent course of disease. Therefore, pre-surgical assessment of TN should improve in order to advance into the era of personalized medicine and identify the best way to manage what has been defined as a 'tsunami of thyroid nodules'.
Aims
The present study has focused on the development of an algorithm capable of inferring TN state of malignancy in order to improve patient' management and avoid inappropriate use of diagnostic procedures.
Materials and methods
Information regarding epidemiological, clinical, biochemical, ultrasound, molecular and cytological data of over 12.000 TN with known histological diagnosis was collected and analyzed with Machine Learning techniques. Specifically, TN were grouped into clusters with similar characteristics using partition clustering algorithms such as K-means e K-medoids, being the latter more flexible to outliers deviations.
Results
The designed algorithm was able to accurately identify malignant and benign TN showing malignant and benign US characteristics, respectively, confirming US high predictability for these categories. Moreover, the majority of TN belonging to malignant or suspected malignant cytological classes showed malignant histology.
Discussion
Our algorithm did not achieve the capability of inferring TN malignancy belonging to the grey zone of indeterminate nodules, where US and/or cytology are not accurate enough. However, it was able to confirm that US is essential since it provides the majority of information and is highly predictive for benign TN and for TN having a cytological diagnosis associated to US characteristics highly suspicious of malignancy. In conclusion, the mathematical model built herein brings insight for future tools that could be used to improve TN management and estimate malignancy probability that underlies the discovery of a TN.

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EP446

Prognostic factor of medullary thyroid carcinoma: Experience of one endocrine center

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Based on the medical records of 311 patients with medullary thyroid carcinoma (MTC) treated in the period 1979–2018, using the Kaplan-Meier method, it was found that the sporadic form and male patients are negative predictors of disease. Other is essential for patients with sporadic form of MTC, because sex has no prognostic value in patients with hereditary forms of the disease. The presence of metastases in regional lymph nodes or distant metastases is a poor prognostic factor and analyzes the significance of the severity of the disease showed that patients belonging to the male sex are also a negative factor on prediction. In determining surgical treatment is necessary to consider the size of the tumor: the presence of carcinoma larger than 2 cm (even proved the absence of metastasis) increases mortality and reduces the survival of patients with MTC. In order to determine the need for prophylactic lateral neck lymph node dissection in patients with MTC with tumors of various sizes a retrospective analysis of the incidence of recurrence and mortality of patients depending on the amount of surgery. The study confirmed the idea that dominates the literature regarding mandatory extrafascial thyroidectomy even for tumors less than 2 cm. When the thyroidectomy and lateral (unilateral or bilateral), the frequency of neck dissection lymph node recurrence and mortality of patients were very high, due to frequent metastasis primarily in the central compartment lymph nodes neck. Rate of recurrence and mortality in patients after an isolated central dissection is low, and all cases of complications or death focused exclusively on patients with tumors larger than 2 cm. In case of the combined thyroidectomy and central and lateral lymph node dissection also observed a small amount of recurrence and death in patients: they were significantly lower compared to the group of patients who underwent thyroidectomy and lateral neck dissection, and is comparable with the group of patients who underwent central neck lymph node dissection. This is most clearly observed in the group of patients with tumors up to 2 cm. Based on the analysis concluded that the MTC larger than 2 cm, even in the absence of lymph node metastasis (from a survey of methods of topical diagnosis) is appropriate in conjunction with thyroidectomy and central spending also bilateral lymphadenectomy.

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EP447

Mixed medullary-papillary thyroid carcinoma with mixed lymph node metastases

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Introduction
Medullary thyroid carcinoma (MTC) and papillary thyroid carcinoma (PTC) are two distinct neoplasms originating from follicular and parafolicular-C cells, respectively. These pathologies have always been considered different from each other in terms of their incidence, their cell origin and their histopathological features. Concurrent occurrence of MTC and PTC in the same patient is an unusual event and its occurrence as true mixed medullary-follicular-derived carcinomas is extremely rare.
Case report
We are presenting a case of 60-year-old man, with history of atrial fibrillation who was referred to an endocrinology consultation after diagnosis of thyroid nodules on cervical ultrasound. At neck examination, thyroid was palpable, without palpable thyroid nodules or cervical adenopathy. Ultrasonographically, a solid nodule with 22 mm (the largest dimension) located in the left lobe (in a multinodular thyroid gland) with irregular margins and microcalcifications; supraclavicular suspicious adenopathy was also noticed. The fine-needle aspiration (FNA) of the thyroid nodule suggested the possibility of medullary carcinoma. FNA of the supraclavicular adenopathy was compatible with medullary carcinoma metastasis. The serum calcitonin thus performed was elevated (428.5 pg/ml; NL: < 14.3), with normal urinary normetanephrines and metanephrines. Patient underwent total thyroidectomy with regional cervical lymph node excision. Histopathologically, the diagnosis of mixed medullary-papillary carcinoma of the thyroid was made, with papillary and medullary component metastases in 12 of the 38 isolated lymph nodes in left region and 8 of the 10 isolated lymph nodes at central region. He underwent ablative treatment with I131 and awaits Genetic consultation.
Conclusion
Mixed medullary-follicular-derived carcinomas are a very rare event in clinical practice, and there is a constant debate whether this event should be considered coincidental or rather the result of a common genetic alteration. It is of extremely importance to make the correct diagnosis due to its prognostic and treatment implications. For papillary thyroid carcinoma, radioactive iodine therapy and TSH suppression therapy may be recommended; the treatment of medullary thyroid carcinoma is essentially based on a radical surgical approach, requiring only levothyroxine replacement therapy. The genetic study of these patients is also pertinent to exclude multiple endocrine neoplasia type 2.

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EP448

Relationship between basal thyroglobuline level before radioiodine treatment and therapeutic response in differentiated thyroid carcinoma

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Objectives
We studied whether the postoperative serum thyroglobulin (TG) basal levels before treatment with I131 (baseline TG) could be related with the response to treatment. We consider the excellent response as the absence of clinical, biochemical disease (undetectable TG and anti-thyroglobulin antibodies AcTG negative) and/or structural disease.
Material and methods
This is an observational study that includes 100 patients with differentiated thyroid carcinoma (CDT) who underwen total thyroidectomy and radioiodine therapy as initial treatment, during 2017 and 2018 in our center, with a minimum follow-up of 12 months. Clinical, radiological and biochemical data have been analyzed during the administration of I131 (after rhTSH stimulation) and in the follow-up (at 3, 6 and 12 months).
Results
It is a cohort of 100 patients (74% women) with an average age of 50.9 (range 23–82) years. Total thyroidectomy was performed in 56% and 44% required lymphadenectomy. 38% of patients diagnosed with Ac antiTg at diagnosis. The most frequent histology in our sample was papillary carcinoma (87%). The TNM classification is: stage 1: 75%, stage 2: 17%, stage 3: 5% and stage 4: 3%. According to the ATA classification, 41% of patients present a low risk of recurrence, 27% an intermediate risk and 22% a high risk. The average mean Tg level in patients with negative AcTg was 10 ng/ml. The 83% of these patients showed an excellent response to treatment, 12 months after treatment. They all presented a baseline TG equal to or less than 3.3 ng/l.
Conclusion
In our study, presenting a baseline TG value greater than 3.3 ng/ml implies an absence of excellent response one year after treatment with I131.

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EP449

Esophageal perforation due to thyroid lymphoma

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Introduction
Primary thyroid lymphoma (PTL) represents about 1–5% of thyroid malignancies and < 2% of extra-nodal lymphoma. The most common subtype is diffuse large B-cell lymphoma (DLBCL) (~ 50% of cases), followed by mucosa-associated lymphoid tissue (MALT) lymphoma, both non-Hodgkin' lymphomas. sophageal perforation is a very rare complication during the course of PTL, characterized by poor prognosis.
Case presentation
A 65-year-old Caucasian woman was admitted to our department due to anterior neck enlargement and compressive symptomatology (dysphagia and hoarseness) during the preceding two months. Her medical history was remarkable for rheumatoid arthritis, treated with methotrexate. On physical examination, she had a stiff, non-tender and diffuse goitre. Thyroid ultrasound showed a heterogeneous sub-sternal goitre, including a 34 mm hypoechoic nodule of irregular margins, in the middle of right thyroid lobe. Fine-needle-aspiration (FNA) biopsy was inconclusive (Bethesda III). A computerized tomography (CT) scan showed severe trachea compression, esophageal dilatation and air bubbles in the surrounding structures (Panel A, arrow). The patient' swallowing capacity was progressively deteriorating and, subsequently, she underwent a total thyroidectomy, which revealed esophageal perforation (Panel B, arrow). Histological diagnosis was compatible with large B-cell thyroid lymphoma of high malignancy grade, in the right lobe. The patient was transferred to the intensive care unit, but she developed acute renal failure and repeated respiratory infections, with a progressive thrombocytopenia and normocytic anemia. Bone marrow biopsy showed infiltration by lymphoma cells, but chemotherapy was not feasible due to the patient' clinical state. She died one month later.

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EP450

Total thyroidectomy can still remain the method of choice in some Bethesda III FNAB cases

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Background
Nonivasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and hyalinizing trabecular tumor (HTT) are a rare follicular- derived thyroid neoplasmas with indolent clinical behavior. These tumors are encapsulated or clearly delimited and distinguished by detail using histopathological criteria.

Method
Description of two cases of these rarer tumors, classified on FNAB Bethesda III AUS/FLUS in the BSRTC 2017 and diagnosed after total thyroidectomy. Results. Two cases of classified Bethesda III with ultrasonography guided FNAB were investigated using molecular genetic methods and histopathology verification: In a 61-year-old man following the category Bethesda III system histopathology investigation detected nonivasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTPs) in the terrain of polynodous nodular goitre. There was only minimum of colloid in the microfolliculles but nuclei were slightly enlarged, non-round and ovrlapping. Molecular genetic investigation found c.182A>G p.(Gln61Arg) in the exon 3. somatic mutation of the gene *NRAS*. In a second patient, a 48-year-old man solitary isthmic nodule classified Bethesda III. The postoperative histological finding expressed suspicion of medullary carcinoma. But angioinvasion was not shown and amyloid staining was negative. Supervision by an experienced thyroid pathologist was required. Immunohistochemistry: calcitonin, CEA- negative; thyroglobulin TTF1-positive, NES dispersive positive. Ki-67 unique pattern of membranous positivity characterizing hyalinizing trabecular tumour. (HTT). Molecular genetic analysis c.394G>Ap.(Glu132Lys) in the exon 4. somatic mutation of the gene *NRAS*. Conclusions. In these two rarer tumours with Bethesda III diagnosis total thyroidectomy was chosen as the best option due to risk of possible multifocal involvement in the terrain of nodular goitre, age and male sex with a longer duration and size progression of the nodules. In case of postoperative histological finding of thyroid malignancy, completion thyroidectomy bears higher risk of postoperative complications and the patient is exposed to greater psychological stress.

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EP451

When levothyroxine is not enough- combination therapy with liothyronine

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Introduction
The treatment of central hypothyroidism with a combination of levothyroxine (T4) and liothyronine (T3) is not recommended for most patients since it does not show an advantage over T4L monotherapy. However, in certain patients who remain symptomatic under replacement therapy with T4L and thyroid stimulating hormone (TSH) within the reference values, combined treatment with T4 and T3 can be tested.
Clinical case
Male, 39 years old, medical history of craniopharyngioma, submitted to surgical intervention with subsequent panhypopituitarism. Medicated with 125 mg levothyroxine, 10 mg hydrocortisone, 0.12 mg desmopressin and monthly dose of testosterone. The patient was admitted for septic shock due to Klebsiella pneumoniae cellulitis, aggravated by pyelonephritis due to Morganella morganni, with acute kidney injury and metabolic acidemia, requiring aminergic support and non-invasive ventilation, being submitted to several cycles of antibiotic therapy. Despite the reversal of the infectious condition and improvement in renal function, the patient remained in comatose state, hypotensive (89–65 mmHg), bradycardic (51bpm) and hypothermic (33.4ºC). Blood test showed hyponatremia (130 mEq), normoglycemia (78 mg/dl), free T4 within the reference values (1.10 ng/dl), but with non-dosable free T3, despite 40 days of 150 mg levothyroxine therapy. A deficient conversion of T4 to T3 was assumed and treatment with 75 mg of T3 was started, showing a remarkable improvement in consciousness after 1 day of therapy and normalization of temperature (37.2ºC), blood pressure (112–60 mmHg) and heart rate (60bpm) after 3 days, having gradually discontinued liothyronine. At the date of suspension with 1.52 ng/dl of free T4 and 2,72 pg/ml of free T3.
Discussion
The patient presented hypothyroidism decompensation secondary to sepsis. Initially, the patient' recovery was expected after normalization of the clinical status and normalization of T4 levels. However, the patient maintained a weakened clinical condition, disagreeing with the analytical data, so a combination of thyroid hormone therapy was implemented. This combination therapy should be performed under close monitoring, given the potency of T3 (3 times more potent than T4). The present case highlights that in patients with severe hypothyroidism, including coma, with poor response to T4 replacement, the combination with T3 may be useful, although not recommended.

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EP452

Ectopic thyroid nodules: Unusual localization

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Introduction
Thyroid ectopy is uncommon pathology. The lingual area is the most frequent localization. The medaistinal localization is rare. We report in this article two cases illustrating this location.
1st clinical case
66-year-old woman operated on for benign breast cysts consulted for progressive chest pain. The clinical examination was without abnormalities. The standard biological assessment was normal. Cervicothoracic CT scan showed two heterogeneous enhancement tissue mediastinal masses, a heterogeneous thyroid gland of normal volume. The surgical procedure consisted of a thymectomy and the anatomopathological study concluded to an intra-thymic ectopic thyroid adenoma.
2nd clinical case
57-year-old woman consulted for a chronic cough. No anomaly objectified at the clinical examination. The biological assessment including thyroid was normal. The CT scan showed formation of the cervicothoracic orifice whose density evoked a thyroid or parathyroid nodule. The mass was excised and the antomopathological study found a thyroid parenchyma with no signs of malignancy.
Comments and conclusion
Transcription factor mutations are implicated in thyroid ectopy. Several locations have been described. The mediastinal localization is exceptional. The presence of a eutopic thyroid is frequently associated with the mediastinal location of ectopia. Clinical-biological euthyroidism is as well. Therapeutically, surgery may be indicated in dyspnoea or other disabling symptoms.

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EP453

Epidemiological aspects of medullary thyroid cancer as a component of multiple endocrine neoplasia type 2 in the Republic of Belarus

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Multiple endocrine neoplasia type 2 (MEN2) is a hereditary condition with an autosomal dominant type of inheritance. It is evident that MEN2 is characterized by the presence of Medullary Thyroid Cancer (MTC) as a permanent symptom, the combination of which with pheochromocytoma and parathyroid syndrome is referred to as MEN-2A syndrome. The aim of our study was the creation of a database of patients with MTC and analysis of the data.
Materials and methods
The study is carried out in the framework of the State Program 'Oncological diseases' on the task 'To develop and implement effective technologies for the diagnostic detection and observation of patients with multiple endocrine neoplasia type 2A'. The selection of participants for inclusion was carried out from the Cancer Register of the Republic of Belarus and the medical documentation of the Republican Center for Thyroid Tumors. Patient' data from 1987 to 12/31/2019 were included.
Results
A database of patients with MTC has been compiled containing information on 591 patients, of which 183 patients died. Currently included 420 (71.1%) women and 171 (28.9%) men. The average age at the moment of diagnosis was 53.1 (43.2–61.8) years; 53.2 (43.7–62.6) years for women

and 52.5 (41.6–59.4) for men ($U=32944$, $P=0.115$). Significant differences in age weren't found among men and women. 76.1% patients (450 people) lived in the city and 23.9% – (141 people) in the countryside. The second tumor was discovered in 7.8% patients (46 people). Based on gender, 8.8% (37 people) of women and 5.3% (9 people) of men had the second tumor ($\chi^2=2.13$, $P=0.145$). A concomitant endocrine tumor was present in 1.7% patients (10 people); 1.4% of women (6 people) and 2.35% of men (4 people) ($F=0.61$ $P=0.433$). *Retrospective died patient' data analysis (183 patients).* Life expectancy after diagnosis was 4.5 (1.4–9.5) years. In a woman (108 people) 4.9 (1.2–10.2) years and in men (75 people) 4.1 (1.5–7.8) years no significant differences were found ($U=3746.5$ $P=0.389$). 18.6% patients (34 people) died within 1 year, 19.7% patients (35 people) lived for more than 10 years. Five-year survival rate is 44.6% (79 patients).

Conclusions

Medullary thyroid cancer is more common in women, the average life expectancy after diagnosis is 4.5 years. A concomitant tumor in 7.8% of patients requires genetic verification of the MEN.

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EP454

Features of the radical treatment of medullary thyroid cancer in the republic of belarus

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The medical and social significance of the Multiple Endocrine Neoplasia type 2 (MEN2) is due to the severity of the manifestations of the disease components, namely the tumor process progression, a high risk of vascular accidents, pathological fractures of the femoral neck/spine, gastrointestinal bleeding, chronic renal failure. Late detection of pathology is associated with high mortality due to medullary thyroid cancer (MTC). Thus, the aim of the study was to establish the characteristics of the clinical course and management of patients with MTC.

Materials and methods

The study is carried out within the framework of the State Program 'Oncological diseases' on the task 'To develop and implement effective technologies for the diagnostic detection and observation of patients with multiple endocrine neoplasia type 2A'. A retrospective analysis of patient data from 1987 to December 31, 2019 was performed. The information was obtained from the Cancer Register of the Republic of Belarus and the medical documentation of the Republican Center for Thyroid Tumors.

Results

A database of patients with MTC has been compiled containing information on 591 patients, of which 183 patients died. Currently included 420 (71.1%) women and 171 (28.9%) men. The average age at the time of diagnosis is 53.1 (43.2–61.8) years; 53.2 (43.7–62.6) years for women and 52.5 (41.6–59.4) for men ($U=32944$, $P=0.115$). In general, 95.6% of cases (565 people) underwent surgical treatment, 32.9% (195 people) radiation therapy and 25.9% (153 people) chemotherapy. Given the severity of the disease and the progression of the tumor process, 14.7% of patients (87 people) had combined surgical, chemotherapeutic and radiation treatments. 10.0% of patients (59 people) were operated and had chemotherapy, 17.2% of patients (102 people) had combined treatment – surgical and radiation therapy. Only surgical treatment was performed in 53.6% (317 patients). Less than one percent had only chemotherapy (4 people), only radiation therapy (3 people), complex radiation and chemotherapy treatment. 16 patients (2.7%) didn't receive radical therapy. In this group the average life expectancy after diagnosis was 0.3 (0.7–0.03) years.

Conclusions

In the Republic of Belarus, surgical treatment is the preferred method for the radical treatment of medullary thyroid cancer. However, a high percentage of combined treatment requires optimization of the early diagnosis of medullary thyroid cancer.

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EP455

Features of thyroid state in patients with type 1 diabetes and chronic kidney disease receiving renal replacement therapy

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Aims

Thyroid function changes are common endocrine disturbance among patients with chronic kidney disease (CKD), including those receiving renal replacement therapy (RRT). The purpose of the study was to study the effect of RRT on thyroid function in patients with type 1 diabetes (T1D).

Materials and methods

Thyroid hormone examination was performed before and after hemodialysis procedures (HD) in 9 patients with T1D (3 men and 6 women). Mean age was 41.21±11.09 yrs, duration of T1D was 28.17±9.64 yrs, duration of CKD was 12.98 (4.41–14.98) yrs. The terms of receiving RRT were 16.8 (8.25–59.34) months. There was a marked decompensation of T1D (HBA1s 8.28±1.57%). Nonparametric statistical methods were used. A P-value <0.05 was considered significant.

Results

TSH levels were higher after HD, but not statistically significant. FT4 levels before the HD procedure were low normal 12.25 (11.38–13.0) pmol/l and significantly increased towards normalization after HD 15.66 (13.59–16.22). FT3 levels before HD were low 3.75 (3.54–3.83) pmol/l and significantly increased after the HD procedure 4.00 (3.82–4.60), however, stayed in low normal range. Before HD 78% patients had low FT3 and 33% low FT4, changing after HD to 33% of low FT3 to and 11%. FT4. Patients differed by AbTPO (54.51 (12.05–74.74) IU/l vs 19.10 (8.61–55.62). TG was significantly lower after HD (10.37 (6.87–30.84) ng/ml vs 9.71 (5.66–32.68). Despite the fact that the levels of AbTG significantly decreased after HD159.02 (25.11–336.35) IU/l vs 156.80 (51.59–352.90), its median values remained in the diagnostic interval confirming the presence of autoimmunity. Ab-R-TSH were lower after HD (0.3 (0.30–0.65) IU/l vs 0.30 (0.30–0.30). No relationship between thyroid hormones and HbA1c in T1D patients with RRT, as well as between the duration of CKD and RRT with thyroid profile were noted. The age of T1D manifestation correlated with levels of FT3 ($\rho=0.493$), AbTPO ($\rho=-0.565$). Duration of T1D correlates with TG levels ($\rho=0.627$).

Conclusion

Revealed changes predetermine the need to assess serum levels of free fractions of peripheral thyroid hormones, as well as hormonal studies immediately after the HD procedure. Low levels of AbTSH-R confirms the absence of influence of autoimmunity on the genesis of thyroid disorders in patients with CKD and RRT.

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EP456

Anxiety disorders in patients with autoimmune thyroiditis

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To date, up to 35% of the young population (25–60 years) in developed countries are subject to anxiety disorders. The use of anti-anxiety agents in clinical practice does not always lead to a lasting effect. The study included patients who initially consulted a neurologist or psychotherapist. With panic attacks. On the Anxiety and Depression Rating Scale (HADS), all patients received 11 points or more. The use of anti-anxiety drugs gave a short-term effect with subsequent deterioration. The study group included 76 patients with anxiety disorders, men-29 (age 33.9 years), women-47 (age 31.7 years). The whole patient an ultrasound of the thyroid gland; to assess the state of thyroid function, the levels of thyroid-stimulating hormone, free T3 and T4 in serum were studied. In all patients, titers of antibodies to tyrnoglobulin and to thyroid peroxidase were determined. According to the results of ultrasound, it was revealed that the total thyroid gland in 55 (72%) patients was within the age norm, in 21 (28%) patients it exceeded the norm by no more than 20%. In 71 (95%) patients, an increase in the intensity of blood flow in the gland was recorded. According to laboratory results, 76 (100%) patients had free T3 (2.5–4.3 pg/ml) and free T4 (0.93–1.7 ng/dl), which is an indicator of the norm. The level of TSH in 44 (58%) patients was within the normal range (0.4–4.0 μMU/ml) and in 32 (42%) it was

within the range of 4.1–6.5 μMU/ml. Tiroglobulin was normal in all patients. All patients had anti-TPO (35–1000 IU/ml). Patients with increased blood flow in the gland, but with normal TSH, 39 (44%) people were prescribed NSAID (ibuprofen 200 mg) twice a day for 14 days. NSAID (ibuprofen 200 mg) twice a day for 14 days and thyroxine at a dosage of 25–50 μg were prescribed to patients with increased blood flow in the gland and increased TSH 32 (42%). for 8 weeks. After that, an ultrasound of the thyroid gland and laboratory tests were performed. During the control, the blood flow in the gland decreased in 60 (79%) patients. TSH levels normalized in 30 (39%) patients. With the HADS scale in 71 (95%) patients, the anxiety level ranged from 4–8, which is a normal indicator, while patients did not receive anti-anxiety drugs. All patients with anxiety disorders need to check the function of the thyroid gland, since its disorders can lead to psycho-emotional disorders.

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EP457

The evaluation of hepcidin in patients with graves' disease

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Introduction
Hepcidin is an acute-phase protein and a key regulator of iron homeostasis. Anemia frequently occurs in patients with hyperthyroidism, while hepcidin may be a potential link.
Objectives
Prospective evaluation of hepcidin serum concentration and other parameters related to Fe homeostasis in group of hyperthyroid patients in the course of Graves' disease (GD) at diagnosis and after restoration of euthyroidism.
Patients and methods
42 (32 women, 10 men) patients met inclusion criteria, aged 42.5±15.1 years. Clinical and biochemical assessment, including hepcidin measurement by ELISA method was performed at baseline (T0) and in remission state (T1). The follow-up was presented for 24 patients.
Results
Hepcidin concentration at T0 was significantly higher if compared to the value during euthyroidism [28.7 (8.1–39.4) ng/ml vs. 7.9 (4.3–12.9) ng/ml, $P<0.001$]. Hepcidin level most statistical significantly correlated with ferritin (rho=0.723) in women at T0. In both men [377 (171–411) vs. 165 (84–237) ng/ml, $P=0.001$] and women [84 (23–104) vs. 35 (16–64) ng/ml, $P=0.001$] a significant decrease in ferritin level was demonstrated following therapy.
Conclusions
Hepcidin level decreases significantly during transition from hyperthyroid state to euthyroidism in patients with GD. The observed changes occur presumably in parallel to iron homeostasis fluctuation, which is expressed by ferritin level decrease.

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EP458

Suspicious thyroid nodule in subacute thyroiditis

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Background
Subacute thyroiditis is an inflammatory condition, most likely of viral origin, which typically presents wit low anterior neck pain, fever and transient thyrotoxicosis. Ultrasonography (US) usually shows a diffuse thyroid enlargement with ill-defined hypoechoic areas.
Case
A 55-year old women was admitted in the emergency room, with 2 weeks of anterior neck pain, cervical compressive symptoms of dysphagia, fever and palpitations. On physical examination a firm 4 cm neck anterior mass was palpable. Thyroid US showed a highly suspicious thyroid nodule in the isthmus/left lobe with 38 mm, apparent extrathyroidal extension, microcalcifications, with absence of intranodular flow in Doppler. A fine needle aspiration (FNA) was performed, with a benign result (follicular cells without nuclear atypia and macrophages). Laboratory results: TSH 0.01 mMUI/l (0.4–4.0), Free T4 3.19 ng/dl (0.93–1.70), Free T3 7.2 (2.0–4.4), erythrocyte sedimentation rate 110 mm (< 20), C-reactive protein (CRP) 26.1 mg/dl (< 20), Thyroid peroxidase antibody (TPO) and TRAb were negative. The patient was hospitalized, there wasn't other site of infection, and the Endocrinology department was contacted due to suspicion of Subacute Thyroiditis and discrepancy between US thyroid nodule description and FNA result. Thyroid scintigraphy wasn't performed due to recent contrast exposure (Neck Computed tomography). The patient was treated with Prednisolone with normalization of thyroid function, fever and apparent involution of thyroid nodule, with resolution of cervical compressive symptoms. After 3 months, Thyroid US showed a massive reduction of the thyroid nodule, with 12 mm, without the worrying aspects of first US. Transient hypothyroidism was noted without the need for Levothyroxine replacement, due to absence of symptoms, with normalization of thyroid function after 8 weeks.
Discussion
We present a case with an atypical presentation of Subacute Thyroiditis with a high suspicious 38 mm solitary nodule, with apparent extrathyroidal extension, mimicking thyroid malignancy. The presence of thyrotoxicosis and the symptoms of neck pain and fever were very suggestive of this disease, and after Prednisolone treatment, the thyroid nodule markedly reduced.

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EP459

Variation of parameters of thyroid function during pregnancy

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Introduction
The basic characteristics of metabolism in pregnancy are changes from anabolic to catabolic conditions. During early gestation, the fetus is dependent on maternal thyroid hormones that cross the placenta. Thyroid disease in pregnancy is a common clinical problem, at least 2–3% of women have thyroid dysfunction. Pre-conceptual education and appropriate diagnosis and treatment of thyroid dysfunction in early pregnancy are of great importance, with the aim of preventing complications during pregnancy and offspring. In the first trimester, the 'normal' range for TSH is reduced to 0.1–2.5 mIU/l, and in the second and third trimester is 3.0 mIU/l.
Aim
The aim of this study is to analyse concentration of thyroid parameters and variations of thyroid function during pregnancy.
Matherial and methods
This study included 77 healthy pregnant women in the first trimester of pregnancy registered in the Center for endocrinology of Clinical Center Kragujevac. Blood samples were collected for fT4, TSH and TPOAb and measured by RIA method.
Results
The mean age of 77 patients was 30.8±4.7 years. The prevalence of autoimmune thyroid disease was 25.9% and positive family history for thyroid disorder was in 9%. When we excluded patients with disorders of glicoregulation, the average serum level for fT4 in first trimester was 10.68±2.16 pg/ml, for TSH was 2.09±1.11 mIU/l, the average serum level for fT4 in the second trimester was 7.58±2.11 pg/ml, for TSH was 2.59±1.47 mIU/l, and the average serum level for fT4 in the third trimester was 7.18±1.48 pg/ml, for TSH was 2.48±1.18 mIU/l. For the first time, we shown reference range for thyroid parameters in our population in trimesters:

parameter *(min-max)*	1. trimester	2. trimester	3. trimester
fT4 (pg/ml)	8.52–12.84	5.47–9.69	5.7–8.66
TSH (mIU/l)	0.98–3.2	1.12–4.06	1.3–3.66

Conclusion
It has been shown that as pregnancy progresses, the value of thyroid parameters decreases.
Keywords: thyroid function, pregnancy.
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EP460

Volume changes of thyroid gland in Graves'disease after radioactive iodine treatment

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Introduction
The study describes volume changes of thyroid gland in patients with Graves'disease (GD) after radioactive iodine treatment in the University hospital in Hradec Kralove.
Patients and methods
Retrospectively, we analyzed 66 patients with GD (57 women and 9 men, mean age 52±13.4 years). Volume of thyroid gland was measured before and 1 year after application of radioactive iodine.
Results
Total decrease of thyroid gland' volume was 56% ($P \leq 0.001$). For detailed analysis we divided our cohort into three subgroups according to the function status one year after treatment: 1. hypothyroidism ($n=39$), 2. euthyreoidism ($n=19$), 3. continues hyperthyroidism ($n=8$). The decrease of 69% ($P \leq 0.001$) was found in the first subgroup, of 58% ($P=0.003$) in the second subgoups and of 15% ($P=0.309$) in the third subgroup, respectively.
Conclusion
The successful therapy respond resulted into significant decrease of thyroid gland volume.
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EP461

Immunoassay interference on thyroid functions tests during treatment with Nivolumab

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Background
Immune checkpoint inhibitors (ICI), anticancer therapy blocking specific molecules expressed in tumor microenvironment, are associated to several endocrine side effects. In particular, the use of PD-1/PD-L1 inhibitors is related to a higher incidence of thyroid dysfunction. The most frequent form of thyrotoxicosis is a destructive thyroiditis, which can evolve into hypothyroidism.
Patient findings
We report the case of an 85 years-old patient, affected by metastatic melanoma and treated with Nivolumab, which experienced a severe ICI-related thyrotoxicosis. The diagnosis was complicated by a biochemical interference on thyroid hormones assay, probably induced by Nivolumab.
Summary
Laboratory examination performed before starting anticancer therapy showed normal thyroid function test. Few days after the second administration, the patient developed a severe thyrotoxicosis. According to destructive thyroiditis, in a short period TSH levels normalized and rapidly increased, but FT4 levels resulted inappropriately elevated. A possible analytical interference has been suspected: the sample has been analyzed with a different immunoassay, which confirmed a severe hypothyroidism with appropriately low FT4 levels. Furthermore, we processed the same blood sample after polyethylene glycol (PEG) 6000 precipitation to remove the macromolecules and after this evaluation, FT4 levels resulted appropriately low. Nine months after starting anticancer therapy, the patient stopped Nivolumab administration. Thyroid function tests performed one month later with the first immunoassay showed normal and appropriate FT4 levels.
Conclusions
The peculiarity of this case is represented by the possible biochemical interference of Nivolumab on FT4 immunoassay. In our hypothesis, Nivolumab should determinate interference on FT4 dosage by a mechanism similar to that reported for anti-FT4 autoantibodies. In our case, the interference detected with the one step immunoassay has not been confirmed using a two-step immunoassay. However, further studies will be necessary to prove the biochemical mechanisms which cause this interference.
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EP462

Thyroid nodules during connective tissue diseases

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Introduction
The association of thyroid nodules and connective tissue diseases (CTD) is not uncommon. The purpose of our work was to describe the clinical, biological and ultrasound characteristics of thyroid nodules during CTD.
Materials and methods
It was a retrospective study (2015–2019) including records of patients with CTD and thyroid nodule in an internal medicine department at Ben Arous regional hospital. Informations regarding thyroid function tests and imaging were recorded.
Results
We included eight female patients among patients presenting connective tissue disease (4% of connective tissue disease which are Sjôgren' Syndrom ($n=127$), Rheumatoid arthritis ($n=35$), Scleroderma ($n=17$), systemic lupus erythematosus ($n=22$) and inflammatory myositis ($n=4$)). The thyroid nodule was diagnosed at a mid age of 54 years old. The diagnosis of CTD and thyroid pathology was done concomitantly in four cases. Seven patients had Sjogren syndrome and one had rheumatoid arthritis. The circumstance of nodule discovery was accidental ($n=4$), in front of clinical thyroid dysfunction ($n=2$), biological thyroid dysfunction ($n=1$) and in another case the nodule was palpable. Four cases were associated with hypothyroidia while the rest patients were in a clinical and biological euthyroid state. Immunologic testing was performed in these four patients and thyroperoxidase antibodies were positive in one case. The diagnostic means was in all cases thyroid ultrasound. The number of nodules was an average of two. The size was less than one centimeter in half of the cases and exceeded one centimeter in the rest with a maximum size of 2.4 cm. The nodules were bilateral in one case, isthmic in another, lower site in the rest of patients. Two thirds of the cases were classified as Eutirads 3, one third as Eutirads 2. All nodules were monitored with a good evolution after 1.9 years follow-up.
Conclusion
Thyroid nodules are a common pathology. Their presence during CTD can be a manifestation of the disease or a simple association. Physiopathology is not yet clear. That' why it is necessary to search them in front of CTD so that we won't miss a nodule which can hide a carcinoma.
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EP463

Radioiodine therapy outcome in patient with toxicmultinodular goiter with concomitant hereditary hasharon hemoglobinopathy

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Aim/introduction
The main purpose of this work was to describe a clinical case of thyrotoxicosis with concomitant HASHARON hemoglobinopathy scrutinizing whether the latter could hinder radioiodine therapy (RIT).
Materials and methods
Patient H., 53 years old, diagnosed with moderate toxic diffuse multinodular goiter. Clinical manifestation of the disease were in summer 2018 (TSH – 0 mIU/ml). Medication with thyrozole (20 mg) was initiated. Thyrotoxicosis recurrence in case of discontinuation antithyroid drug therapy proved.

Instrumental methods of diagnostics was performed prior to RIT: ultrasound signs of nodular goiter (TIRADS 2) mixed with thyroiditis, thyroid volume – 8.6 ml; 99 mTc-pertechnetate scintigraphy shows increased thyroid uptake index – 2.7%. In 2000 patient was diagnosed with some unclear abnormal hemoglobin. Complete blood count was prescribed prior RIT: RBC 4.33 × 10 12/l, Hb 131 g/l, MCV 85 fl, RTC 1.04%; biochemical blood analysis: total bilirubin 24.2 μmol/l, bound 4.8 μmol/l, free 19.4 μmol/l, iron 10.2 μmol/l; according to ultrasound examination of the abdominal cavity and kidneys – no signs of pathology; hemoglobin electrophoresis revealed pathological HbS fraction of 17%. DNA diagnostics of the globin alpha chain genes showed the presence of the missense mutation (Asp47His) in the HBA2 gene, resulting in a heterozygous state, resulting in to the formation of abnormal hemoglobin Hb Hasharon. Thus, the diagnosis of hereditary hemoglobinopathy with the presence (17%) of unstable Hasharon hemoglobin in a heterozygous form was verified.
Results
02.07.2019, RIT with 131I activity of 400 MBq. RIT follow up: monthly monitoring of the level of TSH, free T3, free T4 as well as the levels of red blood cells, hemoglobin, total, indirect and direct bilirubin; the level of TRAb and ultrasound of the thyroid gland – after 3 and 6 months. Hypothyroidism was established at the end of 2 months after RIT. Over the entire observation period (6 months), the patient' condition remained satisfactory. There were no episodes of any anemia or significant increase in bilirubin level. Thus, no side effects after RIT were observed.
Conclusion
Clinical case illustrates the approach of patient' preparation prior to RIT and follow up after RIT in the presence of unstable hemoglobin Hasharon. Taking everything into consideration there is no influence on safety of RIT thyrotoxicosis in patients with similar hemoglobinopathies, however, it individual approach in each case can not be excluded.

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EP464

Functional and autoimmune implications in a group of patients with chronic autoimmune thyroiditis associating periodontal disease

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Introduction
Periodontal disease (PD) is a disease with infectious determinism, initiating inflammatory and autoimmune processes, in intricate evolutionary stages, affecting 10% to 60% of adults.
Objectives
Between chronic autoimmune thyroiditis (CAT) and PD there are observations regarding pathogenic interconditioning.
Material and method
Group 1 ($n=109$ patients) comprised 84 women and 25 men. The mean age was 36±9 years for women and 41±7 years for men. All patients had CAT and PD. Group 2 – was composed of 91 patients with PD, 62 women and 29 men, with an average age of 31±11 years for women and 43±12 years for men, without associated thyroid pathology.
Results
Monofactorial linear regression (Pearson' coefficient) tested the dependency ratios between the simplified oral hygiene index (OHI-S) and the parameters determined in the study group (Group 1): the age of the patients and the paraclinical characteristics of thyroid autoimmunity – TSH, ATPO, ATG.
In terms of patient age, an average interdependence was established between the OHI-S and age ($r=0.62$, $P=0.018$). Thyroid function, estimated by the mean value with the serum TSH level recorded above the normal maximum levels (> 4.2 mUI/ml), determined in terms of hypothyroidism an average interdependence between OHI-S and TSH ($r=0.55$; $P=0.0003$). Taking into account the average values of ATPO and ATG considered individually in the patients of Group 1, there was not shown a proportional relation to the value of OHI – S. Analyzing the relationship between the parameters obtained in the study of CAT characteristics in the patients of the study group by multifactorial linear regression, we found a directly proportional relation between OHI-S and TSH, ATPO, ATG – ab. ($r=0.56$; $P=0.001$). Along with these parameters, their interdependence was much closer considering the age of the patients ($r=0.78$; $P<0.001$). This finding is in agreement with the particularities of expression of the evolution duration of PD, but also of the altered thyroid function during the destructive thyroid autoimmune process.
Conclusions
A unitary concept regarding the etiopathogeny and the interconditioning of periodontal disease in patients with chronic autoimmune thyroiditis remains to be specified, taking into account the individualized expression features of the two diseases with inflammatory/autoimmune mechanism.

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EP465

Down syndrome & metamorphosis of thyroid autoimmunity

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Introduction
Patients with Down syndrome are vulnerable to autoimmune thyroid disease and progression from Graves' disease (GD) to Hashimoto' thyroiditis or vice-versa may be more frequently seen in this population, specially at a younger age. In the last years questions have been raised regarding the distinction of this metamorphic scenario from a single entity: autoimmune thyroiditis with TRAbs that trigger opposite functional actions.
Case Report
A female patient with trisomy of the 21st chromosome was evaluated at age 14 due to thyrotoxicosis. She was diagnosed with GD based on clinical signs/symptoms, elevated FT4/FT3 and supressed TSH with TRAb positivity (TRAb 19.7<1.5 UI/ml) and absence of thyroid nodularity in the US. She was given appropriate dosages of methimazole to maintain euthyroidism until age 18 when treatment was stopped due to raising TSH. Given the sustained hypothyroid pattern she was started on levothyroxine. Primary hypothyroidism due to Hashimoto' thyroiditis was diagnosed at age 20 based on the hypoechogenic thyroid pattern and positivity for serum thyroglobulin and thyroid peroxidase autoantibodies. During the 10 years of follow up, thyroid function tests showed marked fluctuations from supressed to high TSH (< 0.02 to 33 μUI/ml) despite the relatively stable dosages of levothyroxine, FT4 and FT3 within reference range and recurrent denial of non-adherence to treatment. More interestingly, TRAb titres ranged from 71–529 (< 1.5 UI/ml) without clear association of titres with severity of thyroid function status. She is now 32 years old and has been euthyroid for the last year with a stable dosage of 88 mg of levothyroxine, positive TPOAb, TgAb and TRAb. Last US showed a small 5 ml hypoechoic gland with fibrous septa (RL 11 × 9.4 × 24 mm and LL 13 × 11 × 26 mm, AP × T × L), suggesting chronic atrophic thyroiditis.
Conclusions
Autoimmune TRAb positive atrophic thyroiditis is being increasingly recognized. Fluctuations in TSH due to shifting/competing stimulatory and inhibitory TRAbs are typical. We postulate that given the current low thyrocyte mass reserve the patient will maintain a more stable thyroid function. Additional tests as scintigraphy (specially I-123) and functional TRAb assays, unfortunately not widely available, shall be helpful to a better understanding and categorization of autoimmune thyroid disorders.

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EP466

Quality of life in patients with Graves' orbitopathy

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Introduction
Graves' disease (GD) is an autoimmune thyroiditis frequently associated with development of Graves' orbitopathy (GO). As a consequence, patients with GO experience impairment of quality of life (QoL) and social function. The aim of our study was to assess quality of life in patients with GO.
Methods
This is a single-center observational study in an outpatient clinic of autoimmune endocrinopathies at a Tertiary, General, University Hospital. Patients with GO and increased levels of thyroid-stimulating immunoglobulin (TSI>1.75 IU/l) were included in the study. Clinical activity score (CAS score) was evaluated by a single ophthalmologist. The patients were asked to complete a QoL questionnaire at their first visit in the outpatient clinic, before initiation of any treatment. Laboratory tests for TSH, T3, FT4, TSI,

TgAbs, TPOAbs, blood count, liver enzymes and thyroid sonography were performed to all patients.
Results
A total of 17 patients were analyzed, of whom females were 82.4% (14/17). The mean age of the patients was 52.3±11.6 years, median TSI levels were 8.36 IU/l, mean CAS score was 3.12±1.22. Diplopia appeared in 41.2% of the patients (7/17). 23.5% (4/17) of the patients had undergone total thyroidectomy, 11.8% (2/17) had thyroid cancer, and 47.1% (8/17) had other autoimmunities. QoL was not significantly associated with gender, age, diplopia, TSI levels, thyroidectomy, and thyroid cancer (P=NS), but there was a trend with the presence of other autoimmunities (P=0.07). QoL was significantly associated only with CAS score (Pearson correlation was –0.59, P=0.013).
Conclusion
This study showed that the quality of life in patients with Graves' orbitopathy depends on their symptoms severity as expressed with clinical activity score.

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EP467

Diagnostic difficulties in patients with large goiter

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The purpose was to study the possibility of various diagnostic methods in patients with large goiter. In 2016–2018 years 628 people with thyroid diseases was operated. In 69 cases the volume of the thyroid was 100–1200 cm^3. The correlation between thyroid volume and age is weak (0.074033), the duration of the disease is high (0.732455). Evaluation of clinical signs was not difficult, but the examination data and symptoms did not give a adequate picture of the thyroid volume. The diagnostic value of the clinical examination (ROC analisis) was low (AUC=0.743; 95% CI=0.715–0.811; sensitivity=72.1%, specificity=74.0%). All patients underwent ultrasound. The possibilities of US was low: the size, location of the thyroid and its ratio to the surrounding tissues in 84.5% did not correspond to the operating data, especially of chest goiter. In most cases, there was no assessment of tracheal and esophageal compression. There were difficulties in assessing the pathology using the TIRADS, sonoelastography and US with contrasts. The ROC analysis revealed that US was not informative for large goiter (AUC=0.793; 95% CI=0.735–0.832; sensitivity=85.5%, specificity=72.4%). The traditional approach to US as a universal method for diagnosing thyroid pathology has limitations. In this regard, for the clarifying topical diagnostics were used magnetic resonance imaging or multispiral computed tomography. The resolution was increased by bolus image enhancement. The study showed that the discrepancies between MRI and operational data in the size and volume of the thyroid were 13.3%. It was practically possible to establish the capsule and the contours of the thyroid and assess the surrounding tissues (including the esophagus, trachea and lymph nodes) in all patients. Densitometric characteristics of the thyroid were different, which gave additional opportunities for differential diagnosis based on the type of contrast accumulation and removal curve, the time of peak achievement, and the degree of maximum contrast. In multi-node goiter and adenoma, a heterogeneous structure was determined on T1 and T2 VI with a predominance of signal amplification with a gentle decrease. In thyroid cancer, the structure was heterogeneous due to hypointensive inclusions on T2 VI with early signal intensity amplification with an early peak and a long phase of contrast elimination. MRI sensitivity in thyroid pathology was 94.4%, specificity-88.7% (AUC=0.915; 95% CI=0.843–0.974). Based on the study, it was concluded that MRI/MSCT is mandatory for patients with large goiter when planning an operating aid.

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EP468

Etiological profile of hypothyroidism in Nepalese patients

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Background
Hypothyroidism is a common endocrine disorder. Common causes are autoimmune disease such as Hashimoto' thyroiditis, surgical removal of the thyroid, drug induced and radioactive iodine (RAI) ablation.
Aim
The aim of our study was to determine the etiology of hypothyroidism in Nepalese patients.
Method
This is a retrospective study conducted in our opd from May 2015 to April 2019 in which data was collected from the patient record files of the subjects diagnosed with hypothyroidism. A total of 1000 patients with hypothyroidism were enrolled for this study.
Result
The findings of the study revealed that, out of 1000 hypothyroid patient, 83.2% were female and 16.8% were male. Among them 11.9% (n=119) had a family history of hypothyroidism, 0.6% (n=6) had undergone RAI Ablation and 0.4% (n=4) had total thyroidectomy. 0.8% (n=8) cases were congenital and out of them 0.7% (n=7) had thyroid agenesis and 0.1% (n=1) had ectopic thyroid (lingual thyroid). 50% (n=500) cases were autoimmune with antiTPO antibody positivity. In 36.3%(n=363), cause could not be determined.
Conclusion
The most common etiological diagnosis of hypothyroidism in Nepalese patients was autoimmune (Hashimoto' thyroiditis). However, cause could not be determined in many patients.

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EP469

Nivolumab induced relapse of graves' disease: A case report

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Background
Immune checkpoint inhibitors, including anti-programmed cell death-1 (PD-1) antibodies, have become promising treatments for a variety of advanced malignancies. Nivolumab, an anti–PD-1 monoclonal Ab, is an effective treatment of unresectable metastatic melanoma, non–small cell lung cancer, renal cell carcinoma, head and neck cancer, Hodgkin lymphoma, and gastric cancer. These medicines can cause immune-related adverse events (irAEs), including endocrinopathies. Thyroid dysfunction (TD) is a common irAE induced by nivolumab. The TD includes hypothyroidism and thyrotoxicosis, which are generally mild to moderate. The most common endocrine adverse event with anti-PD-1 therapy is hypothyroidism (around 5.9% cases). Thyrotoxicosis is related to destructive thyroiditis in most of the cases. Patients with TgAbs or TPOAbs are prone to develop destructive thyroiditis after initiation of nivolumab treatment. The development of hyperthyroidism owing to Graves' disease is virtually very rare, with only 4 cases reported so far. Here we aimed to present the 5th case of Graves' disease after Nivolumab therapy.
Case presentation
A 75-year-old woman with primary malignant urethral melanoma received three courses of nivolumab at a dose of 240 mg every two weeks. Laboratory tests performed before the 4th course due to the patient' palpitation. Thyroid-stimulating hormone (TSH), free triiodothyronine and free thyroxine level were<0.015 (normal range [NR]: 0.55–4.78) mU/l, 7.44 (NR: 2.3–4.2) ng/l and 2.4 (NR: 0.89–1.76) ng/dl, respectively. Her thyroglobulin (Tg-Ab) and thyroid peroxidase antibody (TPO-Ab) were both positive, while TSH receptor antibody (TRAb) was negative. Thyroid ultrasonography showed enlargement of both thyroid lobes with low echogenicity and increased vascularity. Thyroid scintigram showed an increased and diffuse uptake.
She had been diagnosed with Graves' disease approximately eight years ago and treated medically. Tg-Ab and TPO-Ab were both positive, and TRAb was negative like now. After medical treatment was over, the patient was euthyroid in follow-up and even before PD-1 treatment.
Conclusion
While antibody positivity often causes destructive thyroiditis, differently caused Graves' disease in this case. Also, this is the first case-reported that nivolumab therapy induced a relapse of Graves' Disease.

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EP470

Thyroid Dysfunction in patients with HIV infection

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Background
The incidence of endocrine complications among patients with HIV infection has decreased over the last years owing to widespread administration of combined Antiretroviral Therapy (cART) at early stages of the disease. We conducted a prospective observational study aiming to characterize the effects of cART on thyroid function in a cohort of newly diagnosed treatment-naive male patients.
Materials and methods
Male subjects diagnosed with HIV infection at the Infectious Diseases Unit during the period from 2015 until 2017 participated in the study after informed consent. Thyroid hormones, free thyroxine (fT4) and triiodothyronine (T3), thyroid stimulating hormone (TSH) and anti-thyroid antibody levels were measured at baseline, 12 and 24 months post-CART initiation. CD4 lymphocytes were assessed, as appropriate. SPSS 22.0 was used for the statistical analysis of the results.
Results
Fifty-five men attended their first and second year follow-up visits. All subjects had Caucasian ethnic background; the average age was 36.3±10.3 years, and median duration of HIV infection was 20.5 months (2–132). Two subjects (3.6%) had co-infection with hepatitis B, while 5 subjects (9.1%) had a positive family history for autoimmune thyroid disease. From 30 patients in whom anti-thyroid antibodies were measured, only 4 had positive values (13.3%). Two years after cART initiation, CD4 number increased significantly (578±315 vs 840±332, $P<0.001$) and fT4 level decreased (1.00±0.11 vs 0.96±0.12, $P=0.028$), while no change in TSH levels was demonstrated (2.14±1.33 vs 2.42±1.75, $P=0.145$). The incidence of subclinical hypothyroidism at two-year follow up increased 2.5-fold compared to baseline (4 vs 2 subjects). None of the subjects with subclinical hypothyroidism at baseline progressed to clinical hypothyroidism. Interestingly, subjects with subclinical hypothyroidism had negative anti-thyroid antibodies and no family history for thyroid or other autoimmune disease. Finally, 2 subjects developed clinical hyperthyroidism with positive anti-TSH receptor antibodies (TRAB) at 2 years, one of them presenting a relapse of Graves' Disease.
Conclusions
In patients with HIV infection, an isolated decrease in fT4 levels is observed after cART initiation; yet, no fT4 value falls below the normal range. Subclinical hypothyroidism is the most frequent thyroid disorder while GravesC Disease is the most clinically important, usually as a result of Immune Reconstitution Inflammatory Syndrome (IRIS).

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EP471

Risk factors in graves' disease recurrence after treatment with radioactive iodine

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Introduction
Radioactive iodine (131I) therapy is a safe and cost-effective choice in Graves' disease (GD). Usually only one treatment with ^{131}I is sufficient, however, individual characteristics of the disease can lead to its recurrence. The aim of this study is to determinate the risk factors that influence the recurrence of GD after ^{131}I.
Materials and methods
Retrospective cohort study in 528 patients with GD who did ^{131}I therapy between January/2003 and May/2019. From this sample, 78 relapsed after the first therapy with ^{131}I (cases). 78 patients with therapeutic success (euthyroidism/hypothyroidism 36 months after ^{131}I) were randomly selected, adjusted for age and sex (controls). Statistical analysis in SPSSv.23, with the variables: disease progression, family history of thyroid disease, thyroid function tests, antithyroid antibodies, previous therapy with antithyroid treatment, ^{131}I uptake at 24 h (RAIU-24 h), functioning parenchyma mass and administered activity.
Results
A total of 528 patients were enrolled, out of which 82% ($n=433$) were female and 9% ($n=95$) were males, with an average age of 44±12 years. The recurrence rate was 14.8%($n=78$), on average 11±9 months after the first treatment. With regards to previous therapy, propylthiouracil (PTU) compared to thiamazole, was used more often in patients with recurrence (31.4% vs 6.5%; $P<0.01$), with an odds ratio of 6.67 (95% CI: 2.14–20.41). Recurrent patients had significantly higher T3l (14.9±10.5 vs 8.9±6.3; $P=0.001$), TPO Ab (1107±1505 vs 549±666; $P=0.04$), RAIU-24 h (65±11 vs 61±12; $P=0.02$) and functioning parenchyma mass (75±30 vs 48±19; $P<0.01$). There was a tendency to prolonged illness in recurrent patients (months) (32±10 vs 24±8; $P=0.064$), but without statistical significance. There were no difference between: family history of thyroid disease, TRABs and administered activity.
Conclusion
In this study, the recurrence rate of GD submitted to therapy with ^{131}I was 14.8%, on average one year after the first treatment. The recurrence is significantly associated with higher: T3l, TPO Ab, functioning parenchyma mass and RAIU-24h. Previous therapy with PTU was associated with a significant increased risk of recurrence. The longer the duration of the disease, the greater the tendency for recurring disease.

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EP472

Aberrant cervical thymus mimicking thyroid on ultrasonography: A case report

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Introduction
An abnormally positioned thymus may either be aberrant or ectopic. Aberrant cervical thymus (ACT) is located along the normal pathway of descent of the thymus, with an attachment to mediastinal thymus via thymic tissue or fibrous cord in 50% of the cases. ACT is usually diagnosed within the first and second decade of life, and most lesions are cystic.
Case report
We report a case of 9-year-old woman was referred to our hospital for the operation of thyroid nodule. He did not have any neurological symptoms. During the ultrasonographic evaluation for thyroid thyroid, an incidental solid mass was found, which was located at the lower pole of the left thyroid, without remarkable interface echo to the thyroid parenchyma. Computed tomography (CT) showed a mass located at the lower pole of the left thyroid too. On the surgical field, the mass was found under the left thyroid. The mass was a yellowish soft mass. The mass was confirmed as the thymic tissue without any cystic component.
Conclusion
Its very important to recognize an aberrant cervical thymus as a differential diagnosis of paediatric neck masses, such as cervical lymphadenopathy, branchial anomalies, vascular malformations, inflammatory lesions and neoplasm. Ultrasound and CT scan can help to establish the etiological diagnosis.

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EP473

Pseudomalabsorption as a cause of persistent hypothyroidism

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Introduction
Levothyroxine is the treatment of hypothyroidism, achieving normal thyroid stimulating hormone (TSH) levels. The optimal dose of Levothyroxine may

be affected by several factors such as age, gender, body weight, patient' compliance, some medical disorders and drugs intake. Persistent hypothyroidism secondary to non compliance is rare and represents a diagnostic challenge.
The aim of this study was to describe cases with refractory hypothyroidism due to pseudomalabsorption of Levothyroxine.
Observations
We report three patients who presented with persistent primary hypothyroidism despite high doses of Levothyroxine. All patients confirmed the good compliance with the hormone replacement therapy. An oral dose of 600 µg of Levothyroxine was administered under medical supervision. Baseline thyroid function tests were performed and repeated after 2, 4, 6 and 24 hours. The first case was a 33-year-old man with a hypothyroidism diagnosed 19 years ago. He presented with a refractory hypothyroidism on 300 µg/d of Levothyroxine. The oral lévothyroxine test revealed a persistent high TSH level and low FT4 level consisting with the diagnosis of lévothyroxine malabsorption. The serology of celiac disease was negative. Gastroscopy revealed H. pylori gastritis. After treatment, the patient presented with a persisting refractory hypothyroidism with a TSH levels of 1068 mIU/l and a FT4 level of 0.46 ng/dl on 500 µg of Levothyroxine. The second patient was a 27-year-old woman who was treated with radioactive iodine for Graves' disease. She was on lévothyroxine replacement therapy since 3 years. She presented with a TSH level superior to 100 mIU/l and a FT4 level of 0.51 ng/dl on 250 µg of Levothyroxine. The third patient was a 45-year-old woman who had a thyroidectomy and radioactive iodine for a thyroid papillary carcinoma 4 years ago. She had a TSH level of 26.144 and a FT4 level of 1.04 ng/dl on 400 µg of Levothyroxine. Oral lévothyroxine absorption challenge test revealed a correct increase in FT4 levels and a decrease in TSH levels in all patients. They were diagnosed with pseudomalabsorption, and were advised about compliance. The mean TSH after 3 months was 10.3 mUI/l under lower doses for two patients and same dose for the second one, secondary to a persistent non-compliance.
Conclusion
In the absence of evident causes of persistent hypothyroidism despite optimal doses of lévothyroxine, the oral absorption test under medical supervision is useful to diagnose pseudomalabsorption.

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EP474

Association of the rs12976445 MIR125A polymorphism with the clinical course of Graves' disease in Russian population

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Introduction
Graves' disease (GD) is an autoimmune disorder of the thyroid gland, which is characterisied by a breakdown in immune tolerance. The lymphocytic infiltration of the thyroid leads to production of autoantibodies targeting thyroid stimulating hormone receptor (TSHR). The clinical course of GD varies among patients and it is difficult to predict the relapse risk after antithyroid therapy withdrawal. It is believed that GD occurs due to genetic suspectibility in combinaton with external factors. According to recent studies, microRNAs (miRNAs), which are small noncoding RNAs, also can play crucial role in the regulation of the immune system and development of autoimmunity. The aim of this study was to identify the association between single nucleotide polymorphism (SNP) rs12976445 in *MIR125A* gene and GD recurrence risk in Russian population.
Methods
We enrolled 270 patients with GD (210 women, 60 men) and 200 adults without autoimmune disorders. The mean age of GD onset was 41±13.6 years. In our study we mesuared the levels of TSH, free T4, T3, TRAb before and after 12–18 months of antithyroid drug treatment. Also the ultrasound examination of the thyroid gland was performed. Genotypes of SNP rs12976445 *MIR125A* were identified using direct sequencing and polymerase chain reaction–restriction fragment length polymorphism method. Alleles and genotypes frequencies were compared between groups using the Chi-square or Fisher' exact probability test.
Results
In our study the relapse rate estimated 33%. Only 13% of patients achieved remission of GD. The levels of TSH, freeT4, T3, TRAb did not differ significantly among patients. In this study significant differences in the distribution of alleles and genotypes between GD patients and control group were not revealed ($P>0.5$). Among the patients with the reccurence of GD the CC genotype carriers were significantly more frequent ($P=0.001$, OR=5.5, 95% CI 1.8–13.8) than in patient with GD in remission.
Conclusion
Our results suggest that SNP rs12976445 *MIR125A* is associated with the risk of GD relapse but not with the severity of hyperthyroidism. At first time in Russian population with GD genotypes and allele frequencies of the rs12976445 *MIR125A* were identified.

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EP475

Peculitaries of markers of thyroid homeostasis in patients with liver cirrhosis of non-viral ethiology

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The aim of this study was to assess thyroid homeostasis in patients with liver cirrhosis (LC) of non-viral etiology and analyze the association between serum thyroid parameters and A/C polymorphism in the deiodinase type 1 (DIO1) gene in these patients.
Material and methods
The study was conducted on 70 subjects: 50 patients with (LC) and 20 healthy controls. The thyroid homeostasis was evaluated by using «thyroid function tests», measurement of serum free thyroxine (fT_4), free triiodothyronine (fT_3) and thyroid stimulating hormone (TSH). A/C polymorphysm in the DIO1 gene was studied using a polymerase chain reaction.
Results
The level of fT_3 was reduced by 12.1% ($P<0.01$) in patients with (LC), fT_4 level was increased by 15.1% ($P<0.01$) in group of patients with (LC) compared to healthy controls. These changes, obviously, are the result of a decrease in the activity of DIO1 and inhibition of T_4 to T3 transformation. The theory might be confirmed by significantly reduced fT_3/fT_4 ratio (by 21.6%, $P<0.001$), that decreased below the reference range in 78% patients with (LC). At the same time, fT_4/fT_3 ratio increased by 24.1% ($P<0.001$) compared to healthy controls, that can be attributed to the non-thyroidal illness syndrome in these patients. Elevation of TSH level by 28.7% and TSH/fT_3 ratio by 45.7% were determined in patients with (LC) compared to healthy controls ($P<0.05$). The study did not reveal an association between the genotypes of DIO1 gene and the level of TSH in serum. However, it has been established that the presence of the C-allele was associated with elevation of fT_3 level and fT_3/fT_4 ratio, decreasing of fT_4/fT_3 ratio and fT_4 level, while the presence of A-allele resulted in a decrease in fT_3/fT_4 ratio and serum fT_3 with the increase in T_4 level in patients with chronic hepatitis.
Conclusions
Liver cirrhosis is accompanied by the development of non-thyroidal illness syndrome with a reduction in free triiodothyronine level (by 12.1%, $P<0.01$), an increase in free thyroxine and thyroid stimulating hormone levels (by 15.1%, $P<0.01$ and 28.7%, $P<0.05$ respectively), a decrease in fT_3/fT_4 peripheral conversion rate (by 21.6%, $P<0.001$). Pathological changes in thyroid metabolism are associated with A/C polymorphism in the DIO1 gene.

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EP476

Inaugural cardiothyreosis

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Introduction
Cardiothyreosis or thyrotoxic heart disease is the most dangerous complication of hyperthyroidism. This rare complication can be revealing and occurs mostly to fragile patients ; eldery or individuals with preexisting cardiac troubles.

Observation
We report the case of a 59 years old male without medical history, who consulted the emergency for dyspnea and palpitations due to atrial fibrillation (ACFA) not well tolerated with both respiratory and neurological distress. The patient had amyotrophia, bilateral exophtalmos and a homogeneous goiter with high level of FT4 (48.7 pmol/l) and low level of TSH (< 0.005 µUI/ml). The thyroid ultrasound showed a giant multinodular goiter hyperechoic heterogeneous and hypervascular. The diagnosis of grave' disease was confirmed. We completed the investigation with a cardiac ultrasound that revealed an infero-septo-basal hypokinesia with a left ventricular ejection fraction (LVEF) at 50%. The patient received antithyroid medication associeted to B-blockers with progressive decrease in the doses after clinical and biological control. Two weeks later, the patient was no more in an acute condition and he was discharged.
Conclusion
Hyperthyroidism is a frequent disease, revealed after cardiothyreosis can be associeted with higher morbidity and mortality. The ACFA is its most common clinical form and underlying cardiac disease is often present.

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EP477

Thyrotoxicosis and Tuberculosis (TB) related cervical lymphadenopathies: A case report

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Introduction
Grave´s disease (GD) is the most prevalent cause of hyperthyroidism, leading to inflammation of the thyroid gland and sometimes to an enlargement of the nearest lymph nodes caused by that same inflammatory process. Peripheral lymphadenopathy of doubtful cause presents a diagnostic dilemma. There are many potential causes: biopsy is sometimes the best way to reach a definitive diagnosis. Tuberculous adenitis is usually regional and mainly affects nodes of the head and neck.
Clinical case
A 21 year-old male patient, with no significant past medical history besides rhinitis and active smoking, is sent to Endocrinology clinic (2016) in the setting of laboratory workup alterations: thyroid-stimulating hormone (TSH)<0.008 uUI/ml (0.27–4.2); Free thyroxine (FT4) 3.26 ng/dl (0.7–1.58). He presented to the hospital complainning about sudden weight loss (15 kgs in 2 months), anxiety, palpitations, insomnia and trembling hands for over a year. He denied any prior history of similar symptoms.
Physical examination showed signs of goiter, cervical bilateral lymphadenopathies (III/IV region) and otherwise unremarkable and tiamazol 5 mg bid wasprescribed. Six weeks later, thyroid function tests showed a TSH of 0.12 µIU/ml, FT4 of 0.41 ng/, free triiodothyronine (FT3) 2.3 pg/ml (2.57–4.43), TSH receptor antibodies (TRabs) 15.9 IU/l («1) and thyroid peroxidase antibodies 2902.0 UI/ml (0–34). Thyroid ultrasound was significant for an enlarged, heterogeneous, and-hypervascular gland, consistent with an autoimmune or inflammatory thyroiditis. Multiple cervical lymphadenopaties consistent with reactive nature, probably secundary to the inflammatory thyroiditis. At this point, our patient showed a remarkable clinical improvement but a new onset of excessive tiredness, nocturnal fever and further enlargment of painless cervical lymphadenopathies, led to further testing: cervical-thoracic Computer Tomography (CT-scan) showed cervical, supraclavicular and mediastinum lymphadenopathies; serologies were all negative; peripheral blood immnunophenotyping was negative for proliferative disease; aspiration biopsy cytology of one of the lymphadenopathies was performed (Immunophenotyping was negative for proliferative disease; bacteriological and mycobacteriological were also negative). One of the cervical lymph nodes along with adenoid tissue were surgically removed and the cultural test came out positive por Mycobacterium Tuberculosis. Sputum examination was negative for this agent. The patient initiates TB still under treatment for his now assymptomatic Graves disease (tiamazol 5 mg bid). The latest blood tests revealed: Trabs 9 IU/l, TSH 0.13 uUI/ml, FT4 1.72 ng/dl and FT3 4.01 pg/ml.
Conclusions
This cases teaches us how to never overlook all the possible differential diagnosis associated with lymphadenopathies. Tuberculous adenopathies can ecographycally simulate many other conditions.

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EP478

Recurrent subacute thyroiditis case of an elderly patient

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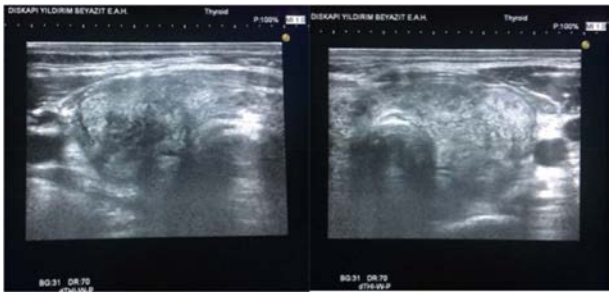
Introduction
Subacute thyroiditis (SAT) is the inflammatory disease of thyroid gland, which commonly affects middle-aged females. SAT is rarely seen in extreme age groups. Herein, we reported an 82-year-old patient presenting recurrent SAT.
Case report
An 82-year-old female patient presented fever, neck pain, weakness, and dizziness. She had hypertension and peripheral vascular disease. She had a 2-week of symptom history and admitted to emergency service before being referred to our clinic. Her body temperature was 38.6 °C and the heart rate was 105beats/minute. The thyroid gland was painful in palpitation. Hyperthyroidism and elevated acute phase reactants were observed. Thyroid ultrasonography showed bilateral hypoechoic heterogeneous areas. The patient having diagnosed SAT was started to use 48-mg methylprednisolone. The dose tapering protocol was 48–32–24–16–8–4 per week respectively. The severity of symptoms was decreased after three days of the initiation of the treatment. After 6-week of the treatment, laboratory and ultrasonography findings were resolved. 2 weeks after the completion of SAT treatment, the neck pain relapsed. Laboratory tests and thyroid ultrasonography were compatible with SAT. 48-mg methylprednisolone was started again with the same tapering protocol. At the end of the second treatment, TSH was 5.82 mIU/l while thyroid autoantibodies were negative. We presently continue to follow up the patient in the second month of SAT resolution.
Conclusion
In the evaluation of large patient groups, SAT was reported in very small numbers in patients whose ages were over 80. Although, the most well-known reasons for the SAT recurrence are short treatment period and genetic background, decreased immune response may be a possible risk factor for elderly patients. The symptoms of SAT can be more exaggerated and the management can be more challenging in elderly patients. Therefore, clinicians should be more careful about the treatment and follow-up of elderly patients with SAT.

Table 1 Laboratory parameters in SAT processes.

	1. SAT	After treatment	2. SAT	After treatment	Reference range
Sedimentation, mm/h	62	6	42	18	0–20
CRP, mg/l	107	1.8	103	2.7	0–8
WBC	9500	10.100	7500	9700	3.57–
TSH, mIU/l	0.12	0.32	1.11	5.82	0.38–5.33
fT4, ng/dl	1.79	0.94	0.93	0.94	0.58–1.6
fT3, ng/dl	4.67	3.1	4.1	4.22	2.66–4.37
anti-TPO, IU/ml	0.3	0.3	0.3	0.2	0–9
anti-TG, IU/ml	0.9	0.9	0.9	0.9	0–4

SAT subacute thyroiditis, CRP C-reactive protein, WBC white blood cell, TSH thyroid-stimulating hormone, fT4 free thyroxin, fT3 free triiodothyronin, anti-TPO anti-thyroid peroxidase, anti-TG anti-thyroglobulin.

Figure 1 Ultrasonographic appearance of SAT.



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EP479

Investigation of aggregation disorders before and after levotyroxin therapy in patients with hashimato thyroiditis

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Objective
Thyroid hormones are powerful mediators of numerous physiological and metabolic processes, including blood clotting, and thyroid dysfunction can adversely affect various stages in the coagulation cascade. Mean platelet volume (MPV) is used to measure platelet size and may indicate platelet activity. Studies have reported that increased MPV is associated with atherosclerotic lesions and cardiovascular diseases, and conflicting results have been reported for the relationship between thyroid function and MPV. In this study, in the healthy control group and patients with hypothyroidism due to Hashimoto' thyroiditis, L-thyroxine treatment was given to euthyroid after at least 6 months of treatment. We investigated its effect on platelet aggregation.
Materials and methods
We evaluated 72 patients diagnosed with Hashimato thyroiditis between March 2013 – May 2018 and who were followed for at least 6 months of L-thyroxine treatment.
Results
A total of 72 patients (61 males, 11 females) were included in the study. The control group consisted of 32 healthy individuals (25 female and 7 male). hemoglobin (Hb), mean erythrocyte volume (MCV), MPV and platelet count (PLT) and thyroid function tests were studied in the patient and control groups. There was no significant difference between patient and control groups in terms of mean Hb, MCV, MPV and PLT ($P>0.05$). There was no significant difference between the pre- and post-treatment Hb values ($P=0.651$) and the mean MCV, MPV and PLT values before and after treatment ($P>0.05$).
Conclusion
Hb, MCV, MPV and PLT values of patients with Hashimoto thyroiditis before and after at least 6 months of L-thyroxine treatment were not significantly different. There was no significant difference between the Hb, MCV, MPV and PLT values of the patient group before and after L-thyroxine treatment for at least 6 months.

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EP480

Laboratory and USG thyroid examinations in the period of 2010 to 2017 in the Slovak Republic

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Objectives
Between 2010 to 2018, the number of patients with thyroid disease in the Slovak Republic grew by 43.4%. We investigated the development of physical, laboratory, USG thyroid examinations and economic costs over the period 2010–2017.
Methods
The study was conducted using data from patient records of the General Health Insurance Company, which registered approximately 3,497,265 policyholders (66.13%) in 2010 and 3,238,500 policyholders (62.01%) in 2017. Laboratory (fT3, fT4, TSH, aTPO, aTG, thyreoglobulin, TRAK) and USG thyroid examinations were evaluated in relation to E00-E07 ICD diagnosis.
Results
The number of patients with these diagnoses had a constant growth tendency: 2010–258 622, 2011–272 936, 2012–284 086, 2013–304 213, 2014–341 496, 2015–349 498, 2016–368 393, 2017–370 745. The same tendency was observed in laboratory examinations and as well USG examinations: 2010–5 407 687 resp 1 382 937, 2011–5 303 433 resp 1 453 508, 2012–5 194 163 resp 1 526 951, 2013–5 391 737 resp 1 629 922, 2014–6 183 108 resp 1 751 184, 2015–6 024 153 resp 1 812 302, 2016–6 361 716 resp 1 913 681, 2017–6 158 735 resp 1 941 145. The total costs of endocrinology, laboratory and USG examinations were: 2010–11 355 988 €, 2011–11 214 956 €, 2012–11 132 859 €, 2013–11 654 875 €, 2014–12 917 370 €, 2015–13 100 799 €, 2016–14 104 543 € and in 2017–14 052 674 €. The average number of laboratory and USG examinations per patient was: 2010–3.57 resp 1.19; 2011–3.48 resp 1.19; 2012–3.29 resp 1.18; 2013–3.16 resp 1.19; 2014–3.10 resp 1.20; 2015–3.04 resp 1.20; 2016–3.01 resp 1.20; and 2017–2.96 resp 1.19.
Conclusions
The possibilities of influencing cost reduction without compromising the quality of health care will be focused on a stricter indication of laboratory examinations, in particular fT4, fT3, aTG, aTPO, TbG, based on the new expert guidelines for diagnosis and treatment of thyroid diseases issued by the Ministry of Health of the Slovak Republic.

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EP481

Is there genetic linkage between benign adenoma and papillary cancer of thyroid: A linkage study through braf and ras gene mutation study

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Introduction
The adenoma- carcinoma sequence in thyroid nodules is an enigmatic phenomenon. Genomics is the only definitive modality to resolve this hypothesis. Adenomas and papillary carcinomas tend to have mutations in RAS and highly specific BRAF gene respectively. In this context, we set out study the prevalence of these somatic mutations in surgical tissue samples.
Material and methods
This prospective study was conducted on surgically managed thyroid nodule patients. Institutional ethical committee approval was obtained. Diagnosis was based on biochemical confirmation, imaging, fine needle aspiration cytology and later confirmed by histopathology. We selected 28 benign thyroid adenomas (BTA) and 24 papillary thyroid carcinoma (PTC) cases. Tumour tissue samples were taken from ex-vivo thyroidectomy specimen within operation theatre. After appropriate processing of samples, DNA extraction, cDNA preparation, PCR amplification, application of 4 sets of Primers were performed as part of mutational analysis of RAS (H-,K-,N-) and BRAF genes.
Results
Homozygous mutations in N-RAS were found in 10/28 (36%) of BTA and 1/25 (4%) of PTC cases. No H-RAS or K-RAS mutations were found in both groups. Homozygous mutations were found in BRAF gene in 3/28 (11%) of BTA cases and 11/24 (46%) of PTC cases. The differences were statistically significant.
Conclusions
N-RAS and BRAF mutations were prevalent in both benign and malignant thyroid nodules giving some evidence for linkage between them. Though not robust, we opine that there is possibility of adenoma- carcinoma sequence in thyroid nodules. BRAF and RAS mutations appear to be specific to PTC and BTA respectively. We need larger multi-institutional studies to justify this observation in future.

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EP482

Treatment with tyroisine kinase inhibitor in thyroid cancer: A single centre experience

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Introduction
Tyrosine kinase inhibitors (TKI) demonstrated clinically significant activity in radio iodine (RAI)-refractory differentiated thyroid cancer (DTC) and in locally recurrent, unresectable and metastatic medullary thyroid cancer (MTC). The natural history of MTC and DCT is quite variable with rates of disease progression ranging from a few months to many years. TKI can be associated with progression-free survival, but is not curative and the side effects may have a significant effect on patient' quality of life.
Objective
Characterization of patients with thyroid carcinoma treated with TKI, followed at the endocrine department of a hospital centre, between 2001 and 2019.
Methods
Retrospective cohort study, based on clinical records of patients with DTC and MTC treated with TKI. Statistical analyses with SPSS.
Results/Conclusion
We obtained 14 patients: 71.4% ($n=10$) female, mean age at the diagnosis: 45.93±13.56 years. 35.7% ($n=5$) papillary carcinoma, 35.7% ($n=5$) follicular carcinoma and 28.6% ($n=4$) medullary carcinoma. One patient with MTC had a genetic confirmation of MEN2. All patients performed total thyroidectomy at diagnosis, five of them performed lymph nodes resection too. Three patients had distant metastases at diagnosis. All patients with DTC ($n=10$) underwent RAI-therapy (cumulative mean dose: 566.4±354.6 mCi). These patients had disease progression with metastases (cervical lymph nodes: $n=7$; distant lymph nodes: $n=4$; pulmonary: $n=7$; cerebral: $n=2$; bone: $n=2$), a median of thyroglobulin-721 ng/l (reference range:1.6–60) and non-radioiodine avid disease. It was decided to perform TKI therapy: sorafenib in 9 patients (800 mg/day) and lenvatinib in 1 patient (24 mg/day). Four patients died due to disease progression; five patients performed a second TKI therapy-lenvatinib [4 dues to disease progression (mean Tg:698 >3682.7 ng/l) and 1 due to side effects of sorafenib], one patient maintains the initial TKI with stable disease. Actually, four patients with DTC are alive, three of them with stable disease. Relative to patients with MTC ($n=4$), it was decided to perform ITK Therapy due to disease progression, namely the presence of metastases (absence at diagnosis): cervical lymph node: $n=3$; distant lymph node: $n=2$; pulmonary: $n=2$; liver: $n=1$; bone- $n=1$). Three patients perform therapy with vandetanib (300 mg/day) and one with sorafenib (800 mg/day). Three patients are actually alive. Side effects of TKI were frequent, mainly gastrointestinal (anorexia-47%; transaminases' elevation-37%, diarrhea-32%), hypertension-47% and dermatologic effects 37%; needing dose reduction (36.8%) or even therapy suspension (10.5%). Optimal management of side effects is essential because they have a significant effect on quality of life and this should be factored into treatment decisions.

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EP483

Thyroid metastases from clear cell renal carcinoma: Presentation of two unusual cases and literature review

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Clear cell renal carcinoma (CCRC) is a tumor with great metastatic capacity, although the presence of metastases in the thyroid gland is very uncommon. Therefore it is important to know the oncological background of the patient and to perform a complete immunohistochemical analysis of the thyroid lesion to obtain a correct diagnosis. Thyroidectomy can be considered in patients with no other metastasis or in those who present compressive symptoms as a palliative measure. We present two cases of patients with clear cell type renal cell carcinoma, without a previously known another metastasis of renal origin and symptomatic goiter containing a nodule that was found to be a metastatic lesion.
Keywords: thyroid gland, renal cell carcinoma, metastatic disease, immunohistochemistry.

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EP484

Clinical presentation and prognosis of patients with medullary thyroid cancer

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Medullary thyroid carcinoma (MTC) is a rare type of tumor that originates from parafollicular C-cells and accounts for 3–4% of all malignant thyroid neoplasms. MTC presents as sporadic (75–80%) or inherited tumors (20–25%). Hereditary MTC is part of multiple endocrine neoplasia type 2 (MEN2). Aim of the study was to describe clinical presentation, prognosis and therapy of sporadic MTC patients. Sixty-seven patients (pts) with histologically confirmed MTC referred to ENETS Center of Excellence of Naples, Endocrinology Unity of Federico II University between 2010–2018 were evaluated. MEN-2-inherited MTC were excluded. Clinical-pathological data, therapy and survival were retrospectively reviewed. Mean age at diagnosis was 51.4±15.1 years. Mean calcitonin concentrations at diagnosis were 4101±7801 pg/ml, resulting above the upper limits of the normal range in all cases, 11% with a slight increase of basal calcitonin had a calcium-stimulated test. Thyroid FNC was positive in 59.6%. Disease stage was I in 37.3%, II in 29.8%, III in 22.4% and IV in 7.4%. First-line therapy was surgery in all cases, radical surgery in 75%. Disease relapse occurred in 20 of those who had radical surgery (29.8%) while a second surgey or more was performed in 8.9%. Systemic therapy included pasireotide in 28.3%, everolimus in 10.4%, vandetanib in 13%. Median PFS was 132 months (95% CI, 61–203). Median survival was not reached. Calcitonin concentrations were increased in all cases at diagnosis but highly variable. MTC patients have substantially a favorable and long-time survival. In patients with metastases many different systemic therapies can be considered.

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EP485

Anaplastic transformation of well differentiated carcinoma of the thyroid gland with muscle metastasis

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Introduction
Anaplastic thyroid carcinoma (ATC) is the most aggressive and invasive histological type of thyroid carcinomas. Frequently, upon diagnosis obstructive symptoms and loco-regional metastasis have already occurred. Presence of distant metastasis in the skeletal muscle in ATC is rare; and there are less than five documented cases reported worldwide.
Case
A 68-year-old Filipino Male, presents with two-month history of pain on the right thigh. He has previous history of Papillary thyroid carcinoma and underwent total thyroidectomy with post-operative radioactive iodine treatment. He was asymptomatic until 11 months post thyroidectomy, when he complained of progressive swelling and tenderness on his right thigh. On initial consult, CT scan of the right lower extremity showed a possible angiosarcoma. Biopsy revealed undifferentiated metastatic carcinoma and immunohistochemical stain is positive for CK7, PAX 8 and TTF-1; denoting anaplastic thyroid carcinoma. Due to the findings, he eventually consulted our institution, on examination there' notable firm non-tender mass about 4 × 4 cm at the left supraclavicular area, and erythematous 6 × 8 cm firm

mass on the posteromedial aspect of the right thigh. Repeated excision biopsy of both masses was performed, during the surgery an invasion of necrotic tissue surrounding the mass was seen. Histopathology of both masses presented anaplastic tumor cells. Total hip disarticulation was done due to severe infection and tumor invasion. Further plans for chemotherapy was not executed due to severe sepsis, and eventually patient succumbed to death.
Conclusion
In patients with previous history of well differentiated thyroid carcinoma, a rapidly enlarging neck mass or even a new mass of unknown origin should be suspected for a more aggressive histologic type of thyroid cancer. Aggressive diagnosis should be immediately performed on these patients, due to the risk of de-differentiation to anaplastic thyroid carcinoma. Keen knowledge is needed for clinicians to prevent misdiagnosis and to avoid delay of treatment.

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EP486

Clinical and epidemiological characteristics of thyroid papilar carcinoma at jerez hospital during a 3 years period (2017–2019)

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Introduction
Papillary carcinoma is the most common form of well-differentiated thyroid cancer (80% of the total). In recent years there has been a significant progressive increase in prevalence.
Objectives
The aim of the study was to evaluate the clinical characteristics of the newly diagnosed papillary thyroid carcinoma at the Sanitary Area of Jerez, as well as to analyze its incidence in recent years.
Material and methods
An observational, descriptive and retrospective study of patients diagnosed with papillary thyroid carcinoma in the Health Management Area of Jerez during a 3 year period (2017–2019). Epidemiological and clinical characteristics were analysed and The American Thyroid Association (*ATA*) classification was used for initial risk classification.
Results
During the study period, a total of 63 patients with papillary thyroid carcinoma were diagnosed: 26 in 2017 (5.83/100,000 inhabitants/year); 20 in 2018 (4.48/100,000 inhabitants/year) and 17 (3.81/100,000 inhabitants/year) in 2019. Of these, 5 cases (7.93%) were microcarcinomas. 74% were women with a mean age at diagnosis of 48.89 ± 14 years. 31% of the patients were obese and 28.8% were overweight. The health area was identified: 47.6% area of Jerez, 44.4% area of Jerez-Sierra and 6.3% of Jerez-Costa. 20.6% were smokers. Regarding the clinical characteristics, 50.8% were symptomatic with a 76.2% of single nodules and an average size of 19.8 ± 10 mm. After surgery, based on the 2015 ATA risk classification, 50.6% were low, 27% were intermediate and 12.7% were classified as hig risk of recurrence. Postoperative RAI ablation was used in 81% of patients.
Conclusions
In our area we found an incidence of papillary thyroid cancer similar to other published series. In most cases the diagnosis is made in early stages.

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EP487

The association between thyroid anaplastic carcinoma and papilar carcinoma folicular version – longer life expectancy?

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Introduction
Anaplastic thyroid carcinoma are highly aggressive solid tumors, with a median survival of less than 6 months after diagnosis. They typically occur in patients who are 65 years of age or older. On the other hand, papillary thyroid carcinoma and follicular thyroid carcinoma are generally indolent, with very few progressive cases.
Case report
A 64-year-old patient with no significant pathological history, known with goiter for about 40 years but without endocrinological evaluation, presented in our department for progressive dysphonia. A total thyroidectomy was performed. Histopathological examination revealed aplastic thyroid carcinoma that associates papillary thyroid carcinoma follicular form. The patient received radioiodine therapy (June 2015) and external, cervical beam therapy (July 2016). Post-surgery, CT scan describes multiple cervical, less than 1 cm, lymph nodes, and two straight pulmonary nodules too small to be characterized, stationary imaging aspect at subsequent examinations. In March 2019, he performed a PET-CT scan that detects a left rib (C6-C7) tumor with high FDG activity – surgery was performed, and papillary metastasis was confirmed. In August 2019, it was treated with a complementary dose of radioiodine. Bone scintigraphy and CT scan performed afterward described small, nonspecific rib injuries: secondary or old post-traumatic or arthritic lesions. In this case, thoracic radiotherapy was postponed due to the high risk for secondary lung fibrosis and the uncertainty of secondary injuries. After iodine therapy, the values of thyroglobulin were undetectable both in suppression and without. It was bisphosphonate treatment and possible SORAFENIB – timed for the moment (normal thyroglobulin). In 3 months, a new CT scan, costal biopsy, or better a PET-CT scan are considered.
Conclusion
Anaplastic thyroid cancer is the rarest yet most aggressive thyroid cancer. Most patients present with a rapidly enlarging thyroid mass, and the majority die within six months of diagnosis. In our patient case, it is considered the association between anaplastic and papillary-follicular variant, with a good, unexpected evolution for the anaplastic component but with secondary dissemination for the differentiated part.

Keywords: thyroid carcinoma, management, secondary injury.
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EP488

Simultaneous papillary and medulary thyroid carcinoma – how to approach?

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Introduction
Papillary thyroid carcinoma (PTC) and medullary thyroid carcinoma (MTC) are distinct neoplasms, associated with different histological findings. Their coexistence in the same patient is a rare event, requiring a different clinical approach.
Clinical case
A 72-year-old patient with no family history of thyroid disease, underwent total thyroidectomy in February 2019, due to toxic multinodular goitre, with no evidence of postoperative complications. The anatomopathological study of the surgical specimen revealed aspects of follicular nodular hyperplasia, with a 6 mm papillary microcarcinoma evident in the right lobe, with areas of classical pattern and a 4 mm medullary microcarcinoma in the left lobe (positive immunohistochemistry for calcitonin). Both lesions did not present foci of lymphovascular permeation or extension to the surrounding soft tissues. Two months postoperatively, patient was revaluated under 125 µg sodium levothyroxine id and presented: TSH 3.13 µUI/ml (0.38–1.33), fT4 12.8 pmol/l (7.9–14.4), Tg 0.31 ng/ml (1.15- 130.77), Anti-Tg Ab 8.7 IU/ml (5.0–100.0), Calcitonin 1.9 ng/l (<9.8) and CEA 1.9 ng/ml (<3.0). At this stage, a therapeutic change was made to 137 µg id levothyroxine sodium. In the cervical ultrasound study, a small amount of tissue, compatible with thyroid residue, was evident in the left locus. At 6 months postoperatively, the patient was revaluated again, showing clinical stability, with analytical study revealing: TSH 1.58 µUI/ml, fT4 14.2 pmol/l, Tg 0.24 ng/ml, Anti-Tg Ab 8.7 IU/ml, Calcitonin 1.8 ng/l (<9.8), CEA 2.0 ng/ml (<3.0), PTH 50.6 pg/ml (12.0–88.0) and assays of urinary catecholamines and metanephrines within the reference limits. The ultrasound study revealed at this stage that residual tissue remained in the left surgical bed, with maintained dimensions. Given the stability, patient continued therapy with 137 mg sodium levothyroxine, with indication for clinical, analytical and ultrasound reassessment in consultation.

Conclusions
The simultaneous occurrence of PTC and MTC is an unusual finding. The follow-up should consider the individual characteristics of both, as they consist in entities with different histological patterns and different clinical evolution. The aetiology of this entity is not clear, however, the possibility of a common tumour pathway should be placed and evaluated in series with a higher number of patients.

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EP489

Thyroglobulin vs imaging in late recurrent metastatic thyroid carcinoma

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Introduction
As the incidence of thyroid cancer is increasing, so are the cases of recurrence with RAI refractory metastasis of thyroid differentiated cancer. We present such a case
Case report
A 77-year-old female with a medical history of papillary thyroid carcinoma recurrence 10 years after surgery with successful 3 RAI sessions and normal thyroid cancer markers after treatment until her recurrence a year ago, with TSH unstimulated thyroglobulin of 199 ng/ml. She had extensive cervical surgery with en-block resection and jugular grafting because of laterocervical adenopathies with Bethesda V suspicion of papillary carcinoma. After surgery we referred her to radio iodine treatment.
Laboratory: thyroglobulin of 255 ng/ml, on stimulated TSH of over 100, thyroglobulin antibodies of 5.8.
Whole body I131 scintigraphy: anterior thyroid recurrence.
She received 160 mCi of I131 and as the thyroglobulin remained high the nuclear imagist ordered more imagining.
The cervical and thoracic CT revealed multiple bilateral secondary lesions in the lungs and large supraclavicular adenopathies, with no other primary tumor.
The abdominal and pelvic IRM was normal.
The oncologist repeated the thyroglobulin and the thyroglobulin was 38.9 ng/dl with a TSH of 16, 6 weeks after radioiodine treatment and the decision was to repeat the CT in 2 months.
The new cervical and thoracic CT showed a progression of the pulmonary lesions so the patient was referred to the nuclear imagist with a suspicion of RAI resistant metastasis.
Conclusion
Typically differentiated thyroid cancer has a good prognostic with 5-year survival rate of over 98%, but almost one third of recurrences become RAI resistant with a 5-year survival of only 19%. There is a BRAF mutation that promotes NIS silence in these cases so it is very important to identify these patients as to avoid unnecessary irradiation and waist precious time that could be used with trying new individualized treatment.

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EP490

Solitary fibrous tumour of the thyroid, features of a very rare tumour: A case report

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Introduction
Solitary fibrous tumor (SFT) is a sporadic tumor, commonly found in the pleural cavity. It is like a large well-circumscribed mass, arising from mesenchymal tissue, with spindle cells proliferation, arranged in various patterns. SFT of the thyroid is exceptionally rare, with only about 28 cases being reported in the international literaterature.
A 34-year-old woman presented in the Department of Endocrinology with the diagnosis of a multinodular goiter. She had no clinical signs or symptoms at that moment. Biological and thyroid function tests were normal. We performed an ultrasonographic examination of the thyroid, which described a solid hypoechogenic nodule in the left lobe (12.13 ml); close imagistic surveillance was recommended. In the next presentations,we noticed the same euthyroid status but an increase in the nodule dimensions ($4.9 \times 5.5 \times 3$ cm) and compression symptoms. Fine needle aspiration biopsy (FNAB) under ultrasound guidation was performed with a favorable result after the Bethesda system. Duet o increasing in nodular size, a total thyroidectomy was done, and thyroid hormone replacement therapy was started. Immunohistochemistry revealed positivity for CD34 marker, CD99, BCL-2, CD 68, negativity for desmin and SMA, and a KI-67 index $<1\%$. The diagnosis was benign SFT arising from the thyroid gland. IGF-2 value was normal; the patient remains well 12 months after excision.
Discussions
Our case is a rare case of SFT of the thyroid, where the patient presented with an asymptomatic slowly increasing thyroid mass in the presence of a benign FNAB. There was no evidence of SFT before immunohistochemistry; the exam highlighted SFT characteristic features, very useful in the differential diagnosis that includes undifferentiated (anaplastic) carcinoma.
Keywords: solitary fibrous tumor, multinodulat goiter, thyroid tumor

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EP491

Incidentally discovered thyroid microcarcinomas in patients undergoing thyroid surgery for benign disease

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Objective
Incidentally discovered thyroid microcarcinomas (TMc) are tumors with a maximal diameter ≥1 cm, indetified during a detailed histopathology examination following a thyroidectomy performed for reasons not pertaining to malignancies of the thyroid gland.
Methods
We included 1555 patients who underwent a total thyroidectomy for benign disease between January 2005 and December 2018. Patients with post-surgical pathology consistent with thyroid cancer with a maximal tumor diameter ≥1 cm were excluded. The incidence of TMc was identified and compared between the different subgroups.
Results
The mean age of the 1555 patients was 53.5 ± 13.8 years and the proportion of women was higher (82.5%, $n=1283$). 1206 patients (77.6%) had a preoperative diagnosis of nodular goiter. 136 cases of TMc were identified (prevalence 8.7%). The majority of cases were papillary TMc (91.2%, $n=124$).
There were no differences in prevalence according to sex (women 8.6% vs. men 9.6%, $P=0.601$) or age (mean age 54.4 ± 12 years in patients with TMc vs. 53.4 ± 14, $P=0.415$).
The prevalence was significantly lower in patients with Graves' disease (5.2% vs. 9.6% in nodular goiter and 9.3% in chronic lymphocytic thyroiditis, $P=0.037$).
Conclusion
In our study the prevalence of TMc in patients who underwent total thyroidectomy for benign disease was 8.7%.
The prevalence was significantly lower in patients with Graves'disease.

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EP492

Clinical profile of patients with solitary thyroid nodules attending tertiary endocrine centre in Kathmandu, Nepal

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Background
Thyroid nodules are common with annual increasing trends worldwide. 5% to 15% of the thyroid nodules is thyroid cancer. The prevalence of thyroid nodule is 3%–7% prevalence by palpation and 19%–67% by high resolution ultrasound. Thyroid nodules are more prevalent in women and older age group. More than 95% of all thyroid nodules are benign.

Aim
The aim of this study is to assess the clinical profile of patients with solitary thyroid nodules in our center
Method
This is a retrospective study conducted in our opd in which data of patients with solitary thyroid nodules was collected from the patient record files. A total of 161 patients were enrolled for this study from April 2018 to April 2019.
Result
The findings of the study revealed that out of 161 patients, 82.20% were females and 16.56% were males, mean age was 47.27(±12) years, mean BMI was 26.85 (±5) kg/m^2. 94.4% were non-smokers and remaining 5.5% were smokers. 46.58% had right thyroid nodule and 50.93% had a left thyroid nodule and 2.48% had nodule in the isthmus. The largest dimension of thyroid nodule was 20.70(±12) mm. The cytological diagnosis distribution as per Bethesda nomenclature were 73.29% benign, 18% malignant (all Papillary Carcinoma), 5.59% non-Diagnostic or unsatisfactory and 1.2% suspicious for malignancy and 1.24% AUS (atypia of undetermined significance) or FLUS (follicular lesion of undetermined significance) respectively.
Conclusion
Prevalence of solitary thyroid nodules was significantly higher in females and obese.
Most of the nodules were benign. 18% solitary thyroid nodules were malignant and all were papillary carcinoma in our study.

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EP493

Prevalence of incidentally finding of papillary thyroid cancer among patients with sporadic medullary thyroid cancer

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Introduction
The coexistence of papillary thyroid cancer (PTC) and medullary TC (MTC) is rare. Previous retrospective studies have shown a prevalence up to 19%. The aim of our study was to assess the prevalence of PTC in patients with sporadic MTC.
Methods
This is a single-center retrospective study of an endocrinology outpatient clinic at a Tertiary, General, University Hospital. Patients who had undergone total thyroidectomy with central neck compartment and had histologically confirmed MTC were included in the study. Also, a RET oncogene analysis was performed in all patients. Patients with positive RET were excluded from the study.
Results
A total of twenty-seven patients were analyzed, of whom females were 40.7% (11/27). The mean age of patients was 58.19±13.1 years. The prevalence of PTC was 33.3% (9/27). 22.2% (6/27) of the patients underwent re-operation for lymph node invasion. Distal metastases appeared in 14.8% of the patients (4/27).
Conclusion
According to our data the prevalence of PTC as incidental finding in patients with MTC is higher compared to previous studies. The cause underlying the phenomenon of MTC and papillary PTC is still unclear.

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EP494

Clinical profile of thyroid cancer patients attending a tertiary endocrine center in Nepal

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Background
Thyroid cancer is the most common malignant disease of the endocrine system. Thyroid cancer represents above 1% of all malignancies. There is a paucity of data on thyroid cancer in Nepalese patients.
Aim
The aim of this study is to explore clinical profile of thyroid cancer patients diagnosed and managed in our center.
Methods
A total of 70 patients with thyroid cancer were included in the sample from March 2013 to December 2019. The OPD records of these patients were reviewed for their clinical profiles including age, sex, operation procedure, location of tumor, TNM staging, ATA risk category, RAI ablation and dose of RAI ablation. The collected data was analyzed by using descriptive and inferential statistical with SPSS version 20.
Result
The findings of the study revealed that 81.4% were females and 18.6% were males. The mean age was 37.3(±9) years and mean BMI was 27(±4) kg/m^2. Location of tumor in left lobe was 34.28%, right lobe was 52.85% and both lobes were 12.87%. Among those patients 25.71% had righthemithyroidectomy, 10% left hemithyroidectomy and 64.29% total thyroidectomy. All had papillary thyroid carcinoma. According to American Thyroid Association (ATA) Risk Stratification System, 62.85% had low risk category, 35.71% of patients intermediate risk category and 1.44% high risk category. According to TNM classification, 14.2% patients had stage T1a, 38.5% stage T1b, 32.8% stage T2, 11.5%, stage T3a, 1.5% stage T3b, 1.5% stage T4a respectively.18.5% of patients underwent RAI ablation. Doses of RAI given to patients were 100 mCi (5.7%), 121 mCi (1.42%), 150 mCi (1.42%), 64 mCi (1.42%), 65 mCi (4.28%), 80 mCi (1.42%) and 95 mCi (1.42%). Mean dose of RAI was 96.42 mCi.
Conclusion
Thyroid cancer was mostly seen in females and young age. Most patients had right lobe cancer. More than half of the patients had total thyroidectomy. Most patients had low risk category. Only 18.5% patients underwent RAI ablation.

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EP495

Risk stratification of Bethesda III category thyroid nodules: Tertiary centers experience

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Background
AUS/FLUS (atypia/follicular lesion of undetermined significance) carries a malignancy risk reaching up to 50%. Based on the reported malignancy rate in a given population, the clinical practice towards such a category varies. We hereby identify clinical parameters for risk stratification to aid in decision making for either surgical referral or a clinical follow up.
Our aim is to calculate the malignancy risk in Bethesda III category and to identify clinical parameters that guided both clinicians and patients at our institutions to reach a clinical decision.
Methods
A retrospective review of patients with Bethesda III category thyroid nodules from tertiary centres in the Emirate of Abu Dhabi during January 2011 through December 2015 was carried out. Malignancy risk in Bethesda category III nodules and repeat FNA utility were calculated. Parameters guided referral to surgery were studied.
Results
Two hundred and two cases were included in the study. Of these, 101 cases underwent surgery initially following the first FNA and 10 cases following FNA repeat. Histology confirmed malignancy in (41%) of cases that went initially to surgery and in (40%) of cases that underwent a repeat FNA. Repeat FNA resulted in, 17 (44.74%) cases being re-classified into benign category, 10 (26.3%) being AUS/FLUS category, 6 (15.7%) being both suspicious and malignant, and 5 (13.16%) being unsatisfactory. Repeating FNA resulted in a definitive diagnostic utility in 50% of the cases.
Conclusion
The relatively high malignancy rate in our institutions, the suspicious radiographic features and the repeat FNA predictive value stratified Bethesda III category nodules for appropriate referrals to surgery.
Keywords: AUS/FLUS, thyroid FNA, thyroid cancer, Bethesda category III

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EP496

Thyroid malignancy among patients with thyroid nodules in the united arab emirates: A five-year retrospective tertiary centre analysis

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Objectives
Thyroid malignancy constitutes the sixth common cancer type in the United Arab Emirates (UAE). There are no epidemiological data outlining the prevalence of cancer in thyroid nodules, nor previous analysis of ultra-sonographic features correlating with thyroid malignancy in the UAE. This study aimed to estimate the prevalence of thyroid malignancy in patients with thyroid nodules and to describe the ultra-sonographic characteristics of thyroid nodules harbouring malignancy.
Methods
A retrospective electronic medical records review of all thyroid nodules in patients (aged 18 to 80 years) with normal thyroid-stimulating hormone (TSH) levels, who underwent ultrasound guided fine needle aspiration cytology (UG-FNA) at Sheikh Khalifa Medical City (SKMC) during 2011–2015.
Results
436 patients with normal TSH underwent UG-FNA cytological examination of thyroid nodules ($n=555$ nodules). The overall crude prevalence of thyroid cancer among patients was 10.1% (95% CI 7.5–13.3). The age-adjusted prevalence of thyroid cancer among UAE nationals, Arabs, Far East Asians, and Caucasians were 9.6% (3.6–15.6), 10.0% (6.2–13.8), 16.8% (4.5–29.0) and 16.3% (1.7–30.9), respectively. The crude prevalence was 14.5%(95% CI 6.2–22.8) in men, and 9.3%(95% CI 6.3–12.2) in women. The echogenicity features were significantly different between the cancerous and noncancerous nodules ($P=0.025$). Cancerous nodules were relatively more hyper- and hypo-echoic, while noncancerous nodules were mostly complex.
Conclusion
We report a higher prevalence of thyroid malignancy among patients with thyroid nodules relative to that reported in other parts of the world. The rate of thyroid malignancy was higher in patients of Far-East Asian and Caucasian ethnic background.
Keywords: thyroid, thyroid nodules, thyroid cancer, cancer, prevalence, united arab emirates

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EP497

Mandibular metastasis revealing a vesicular carcinoma of the thyroid: A case report

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Introduction
Oral metastases are exceptional, representing about 1% of cancers of the oral region. The most common primary tumors are the lung in men and the breast in women. Thyroid carcinoma accounts for approximately 3% of all oral metastatic carcinomas.
We are reporting a case.
Observation
65-year-old woman, followed for 35 years for a toxic large goiter at the expense of the right lobe under medical treatment, which consults following a bulky left mandibular mass. The scanner of the face finds an hypervascular tumor process of the lysing left masticatory space completely the rising branch of the mandible, the biopsy of which returns in favor of a secondary localization of papillary carcinoma of the thyroid TTF1 + TG +. The cervical ultrasound shows a voluminous right nodule classified EU-TIRADS III, the fine needle aspiration of which is an income in favor of papillary carcinoma. The extension report doesn't find other locations. The patient benefits at one time from a total thyroidectomy and resection of the mandibular mass. The pathology study returns in favor of a vesicular thyroid carcinoma of 6.5 cm with mandibular metastasis classified PT3N0M1.
Discussion
Distant metastases from differentiated thyroid carcinomas are rare, the most common being the lung and bone (vertebrae, pelvis and ribs). Oral metastases are exceptional, affecting the mandible more often than the maxilla and are rather the plume of vesicular carcinomas due to hematogenous spread. These metastases cloud the prognosis with a 5-year survival rate of 40% and a 10-year survival rate of 27%.
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EP498

A case of graves disease with hepatic dysfunction, thrombocytopenia and paralysis

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Background
Graves' disease is an autoimmune disease that is characterized by production of excess thyroid hormones by thyroid gland, which is called hyperthyroidism. Generally, clinical presentations of Graves' disease range from asymptomatic disease to overt symptomatic hyperthyroidism with heat intolerance, tremor, palpitation, weight loss, and increased appetite. Single-cell lineage haematological abnormalities, such as anemia, leukopenia, and thrombocytopenia, although uncommon, could be part of the clinical manifestations in patients with Graves' disease. Another rare clinical manifestation of hyperthyroidism may occur in the gastrointestinal system, including liver function tests, particularly high serum alkaline phosphatase concentrations. Thyrotoxic patients also may have numbness and weakness in lower limbs.
Case presentation
A 37-year-old male patient admitted to our clinic with palpitation, tremor, abdominal pain, nausea, vomiting, weight loss and dysphagia. Also, he had numbness and weakness in lower limbs. He was afebrile, had tachycardia (110 beats/min), and had a normal blood pressure of 116/65 mm Hg. He had a fine tremor and palpable goitre on physical examination. There were no signs of ophthalmopathy or pretibial myxedema. Laboratory investigations revealed suppressed thyrotrophin (< 0.008 mu/l) and elevated free thyroxine (6.75 ng/dl), mild thrombocytopenia (131×10^9), normal serum electrolytes except mild hypokalemia (3.4 meq/l). The alkaline phosphatase and the gamma glutamyl transferase levels were elevated approximately 3–4 times the upper limit of normal with high bilirubin levels while aspartate aminotransferase and alanin aminotransferase were normal. Thyroid ultrasonography revealed chronic thyroiditis compatible with Graves disease. Thyroid receptor antibody was positive. Other causes of liver dysfunction and thrombocytopenia were ruled out. The patient was started on methimazole 20 mg/day and propranolol 40 mg/day. Complaints of the patient regressed with the improvement of cholestatic enzymes and thrombocytopenia.
Conclusion
Rare clinical manifestations of Graves' disease such as thrombocytopenia, liver dysfunction, muscle weakness in the lower extremities, and mild hypokalemia were present in this patient. All of these findings improved with anti-thyroid therapy.
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EP499

Endocrinopathies related to immune checkpoint inhibition: A clinical case presentation

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Introduction
In the area of Immunotherapy, immunological checkpoints, such as CTLA-4, PD-1 or PD-L1, are membrane proteins involved in the immune response that, when inhibited, cause an increase in T cell activity and a consequent anti-tumor effect. However, this inhibition can also cause adverse effects, including endocrinopathies, such as thyroid dysfunction and hypophysitis.
Clinical case
59-year-old man, diagnosed with lung cancer, treated with nivolumab (anti-PD-1), with complaints of fatigue, decreased muscle strength, anorexia, constipation and depressed mood a month after treatment initiation. Laboratory evaluation revealed autoimmune hypothyroidism and secondary adrenal insufficiency (thyroid stimulating hormone: 7.81 μU/ml; free thyroxine: 0.65 ng/dl; anti-thyroid peroxidase antibodies: 185 U/ml; adrenocorticotropin < 0.1 pg/ml; cortisol: 0.5 μg/dl). It was made a magnetic

resonance imaging that revealed an enlarged pituitary gland, without associated lesions. Following the diagnosis of primary hypothyroidism and adrenal insufficiency secondary to hypophysitis, the patient received replacement therapy with clear clinical and laboratory improvement.
Discussion
The clinical case describes an uncommon association of hypothyroidism and hypophysitis associated with anti-PD-1 therapy and aims to highlight a recent and often underdiagnosed clinical entity: endocrinopathies related to immune checkpoint inhibition.
In cancer patients receiving anti-PD-1, anti-PD-L1 or anti-CTLA-4 drugs, regular endocrine assessment is recommended to make early diagnosis and treat appropriately. The endocrine laboratory evaluation should be performed before starting to immune checkpoint inhibition therapy as well as during the treatment cycle. The hypothalamic-pituitary-thyroid and hypothalamic-pituitary-adrenal axis are the most frequently affected. The remaining assessment of the pituitary function will depend on the clinic of each patient. The therapeutic approach consists of hormonal replacement of the deficient endocrine axis.
Conclusion
The early diagnosis of endocrinopathies as well as the timely institution of adequate therapy can have a significant impact on the prognosis and quality of life of these patients.

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EP500

Is it Graves orbitopathy?

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Graves' orbitopathy, is a rare and potentially sight-threatening ocular disease that sometimes occurs in patients with euthyroid or hypothyroid chronic autoimmune thyroiditis. We relate a case of a man with 53 years that have diabetes and hipertension and regular clinical exams with endocrinologist and oftalmologist. He developed a bilateral exoftalmia, larger at right eye, in 3 months of follow up, without another signs of thyrotoxicosis. After 2 years of follow up, the thyroid function was normal but the levels of thyrotropin (TSH) receptor (TSHR)-stimulating autoantibodies was insistently in very high levels. It was not observed clinical activity on eyes and more involvement of the muscles of eye motility. We discuss the possibility of thyroid-associated ophthalmopathy and some new described causes as IgG4-related disease, neoplasias and others.

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EP501

Early diagnosis of acromegaly in chronic thyroiditis-case report

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Introduction
Acromegaly is characterized by a pituitary adenoma with excess secretion of GH and IGF-1 hormones. More than 90% of the cases are diagnosed as macroadenomas, after 5 to 10 years of clinical manifestation.
Case report
We present the case of a 49 years old man with minor thalassemia, hospitalized in endocrinology department for a routine check of chronic autoimmune thyroiditis. A careful anamnesis showed that in the last year the patient was dizzy, the ring was not fitting on his finger and the shoes were tight. Laboratory findings: elevated IGF1 (617 ng/ml, normal range: 67–225 ng/ml), lack of GH suppression with oral glucose tolerance test (GH = 6.332 ng/ml, normal less than 1 ng/ml), HbA1c = 6.1% (4.8–5.7). MRI of the pituitary gland showed a 7.3 × 5 mm pituitary adenoma. Pituitary-gonadal axis was not affected nor optic chiasm. A thyroid ultrasonography was performed and a 1.48/1.01/1.29 cm nodule was discovered in the left lobe. The thyroid function was in normal range without medication, except thyroid peroxidase antibodies which were elevated. The patient underwent transsphenoidal adenomectomy with good result after surgery (IGF-1 = 259.50 ng/ml –postoperative and 3 months after surgery IGF-1 = 180 ng/ml with GH suppression with oral glucose tolerance test). The diagnosis of acromegaly was also confirmed histopathological. A fine needle aspiration biopsy of the thyroid nodule was performed and it was classified as Bethesda III. Also, the patient underwent screening for cardiomegaly, colon cancer, diabetes and sleep apnea and all were negative.
Conclusion
Diagnosis of GH-secreting pituitary adenoma as microadenomas increases the chance to cure the disease and improves the quality of life. In addition, patients do not develop other complications associated with excess of growth hormone. Early diagnosis is the key in the treatment of acromegaly.

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EP502

Size does it matter?

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Introduction
Thyroid cancer is the most common malignant endocrine tumour and represents 1% of all malignancies. Cancer Research UK in 2015 reported 3528 new cases and 382 deaths with annual incidence of 5.1 and 1.9 per 100,000 women and men respectively. The incidence is increasing globally, mostly due to papillary thyroid cancer.
Ultrasound is the preferred examination with recommended U1-U5 grading system +/- fine-needle aspiration cytology (FNAC).
Results
We present a case of a 28-year-old female with a long history of seizure-free epilepsy who was referred to an endocrinologist with a 3-month history of hot flushes, night sweats and difficulty losing weight. Clinically there was no signs or symptoms of infection, inflammation or any endocrinopathies, expect for palpable nodules on both lower poles of the thyroid. There were no thyroid or carotid bruits audible. She was clinically euthyroid.
A series of investigations showed normal full biochemistry, haematinics, thyroid function, inflammatory markers however, a raised serum basal cortisol which was likely related to the oral contraceptive pill. Subsequently, ultrasound of the thyroid showed nodules in the right lower lobe and a dominant nodule in the left lower lobe measuring 21 mm × 8 mm with moderate vascularity and no macro or microcalcification. Several small cervical lymph nodes on the right side of the neck level III were seen, likely reactive. FNAC of the left dominant thyroid nodule confirmed Thy2.
On subsequent visit, repeat ultrasound of thyroid and FNAC was advised in view of the size of the left thyroid nodule, which confirmed Thy5.
She underwent a total thyroidectomy with an uneventful recovery and was commenced on levothyroxine.
Conclusion
This case highlights the size of a thyroid nodule may well correlate to the likelihood of malignancy. This has been emphasised in American Thyroid Association management guidelines, but not in the United Kingdom.

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EP503

'Thank you for giving me my wife back' – the role of liothyronine (T3) in primary hypothyroidism

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The British Thyroid Association executive committee advised in 2015 that there was insufficient evidence that levothyroxine(T4) and liothyronine(T3) combination therapy was superior to levothyroxine monotherapy, which remains the standard treatment of primary hypothyroidism. It was considered an experimental approach in symptomatic patients on T4 therapy with a TSH level within normal range.
We present a 47-year-old lady who had been diagnosed with primary hypothyroidism for three-and-a-half years under the care of her General Practitioner. Despite treatment with levothyroxine 25 and 50 micrograms on alternate days she had ongoing lethargy, generalised weakness, a lack of concentration and 'brain fog'. She gained over 10 kg in weight over the

previous 5 years despite adhering to calorie intake recommendations, increased exercise regimes and seeing a nutritionist.
On clinical examination, she had a body mass index (BMI) of 36 with a slow relaxing phase of bicep reflexes, an otherwise normal examination of all systems with no overt features of Cushing's Syndrome. She was clinically and biochemically euthyroid with TSH 4.49 mU/l [Normal range (NR) 0.35–5.5], free T4 17.3 pmol/l (NR 10–19.5) and free T3 5.1 pmol/l (NR 3.55–5.44) with positive TPO antibodies. An overnight dexamethasone suppression test excluded a Cushing's syndrome with an appropriate serum basal cortisol suppression at 24 nmol/l.
She was reviewed a number of times over the following 12 months with ongoing symptoms as per patient; feeling tired, worn out, unable to keep awake and 'at her wit's end'. She remained clinically and biochemically euthyroid with free T3 4.3 pmol/l at lower half of the normal range, normal TSH 3.96 mU/l and a normal free T4 15.7 pmol/l, hence no changes to levothyroxine dose were made.
The pros and cons of T3 therapy were discussed in detail and subsequently liothyronine 10 micrograms daily was initiated. At further clinic reviews four and eight months later, she reported a significant improvement in her energy levels, hair growth at her eyebrows and weight reduction of 3 kg with no change in her lifestyle. Liothyronine 10 micrograms daily in combination with levothyroxine 25 and 50 micrograms alternate days was continued with subsequent further improvement in her general wellbeing.
Conclusion
We present a case of significant improvements in a patient's symptoms, well-being and quality of life on commencement of T3 in addition to T4 despite prior normal thyroid function tests on T4 alone.

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EP504

The relationship between thyroid function and lipid metabolism – is it so obvious?

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Introduction
Thyrotropic hormone (TSH), triiodothyronine (fT3) and thyroxine (fT4) affect adipocytes and HMG-CoA hepatic reductase, indirectly regulating the body's lipid metabolism. This mechanism is already known, however the principles of regulating lipid metabolism through thyroid metabolism constitute an important and a desirable element of scientific research in thyreology. Thyrotropic hormone (TSH), triiodothyronine (fT3) and thyroxine (fT4) affect adipocytes and HMG-CoA hepatic reductase, indirectly regulating the body's lipid metabolism. This mechanism is already known, however the principles of regulating lipid metabolism through thyroThe aim of the study was to assess the relationship between TSH, fT3 and fT4 concentrations and lipid parameters, as well as to identify differences in individual thyroid gland dysfunctions.m constitute an important and a desirable element of scientific research in thyreology.
Material and methods
The medical records of 1470 patients were analyzed (gender, TSH, fT3, fT4, total cholesterol, HDL-C, LDL-C, triglycerides as well as the percentage of HDL-C and LDL-C relative to total cholesterol level). Patients receiving statin therapy were excluded from the study. The collected data was statistically analyzed using the STATISTICA 13.3 statistical package
Results
TSH correlated with total cholesterol ($r=0.10$), LDL-C ($r=0.08$), and triglycerides ($r=0.10$), but not with HDL-C ($P=0.43$). fT3 correlated with total cholesterol ($r=0.13$), LDL-C ($r=0.12$), HDL-C ($r=0.29$), but not with triglycerides ($P=0.16$). Correlations regarding TSH were stronger in men, while those related to fT3 and fT4 – in women. Hypothyroidism is associated with a 37% higher risk of triglyceridemia and a 41–62% risk of atherosclerosis compared to the euthyroid population. Full results will be presented during Congress.
Conclusion
The function of the thyroid gland has a significant impact on the lipid metabolism. Correlations between thyroid and lipid parameters show significant diversity based on gender. Full conclusions will be presented during the Congress.

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EP505

Hypothyroidism, a rare complication of nephrotic syndrome: A case report

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Introduction
During nephrotic syndromes, thyroid function abnormalities may be observed. Hypothyroidism due to loss of thyroid hormones or their binding proteins can be seen but remains a rare complication of nephrotic syndrome. We report the case of 22 year old patient admitted for massive proteinura with nephrotic syndrome that was complicated with hypothyroidism.
Case report
We report the case of 22 year old patient who presented with generalized edema. The patient was diagnosed with nephrotic syndrome with massive proteinuria at 15 g/24 h. He was found to have a hypothyroidism with a TSH level at 6 mUI/l. Thyroid ultrasound was normal with negative anti-thyroperoxidase antibodies. A kidney biopsy revealed features consistent with minimal change renal disease. Given the massive proteinuria and etiology investigations of hypothyroidism that were negative, the patient was not put on thyroxine therapy. The evolution was favorable with regression of proteinuria to 5 g/24 under symptomatic treatment and normalization after a month as well as thyroid function.
Discussion
Excessive loss of urinary proteins due to nephrotic syndrome leads to loss of albumin and thyroxine binding globulin (TBG) through urine and can affect thyroid function. It also damages renal tubules and reduces the reabsorption of low-molecular-weight proteins, including free thyroid hormones. In most cases, the loss of thyroid hormones is compensated by an increase in TSH. Hypothyroidism, which remains a rare event during nephrotic syndrome, is seen mainly in massive and prolonged proteinuria.
Conclusion
The occurrence of hypothyroidism in nephrotic syndrome in adults is rarely described. Its exact prevalence is not well known. It seems useful to systematically assess thyroid function in the nephrotic syndrome especially if the proteinuria is massive and prolonged.

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EP506

Hashimoto's tiroiditis, quervain's disease and a suspicious nodule

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Introduction
The Quervain's disease is an infrequent subacute thyroiditis (ST) that results in granulomatous infiltration of the gland's parenchyma. Is usually diagnosed clinically based on cervical pain, systemic symptoms, altered thyroid function tests (TFTs) and history of upper respiratory tract infection. It is a benign self-limited condition that may share US features with malignancy which may result in improper therapy, including lobectomy.
Case report
A 47-year-old female was evaluated due to the identification of a macronodule not present in the previous year US. She had primary hypothyroidism substituted with 100 mg of levothyroxine. Previous exams (2018) showed negativity for anti-thyroid antibodies and a small sized gland without nodularity, suggestive of chronic thyroiditis. The ultrasound performed in the context of mild cervical pain (5/2019) revealed relative enlargement of the right lobe and a taller-than-wide 28 mm markedly hypoechoic, heterogenous nodule with poorly defined margins.
During medical interview (9/2019) she denied risk factors for thyroid cancer or history of respiratory infection. She complained of right-sided cervical moderate pain exacerbated by touch, that started 4–5 months before and lasted 2–3 weeks. She denied any other local signs/symptoms, viral or thyroid dysfunction associated systemic symptoms apart from a period of exacerbated anxiety in these previous months.
Upon inspection and palpation there were no inflammatory signs, the gland had normal size, no palpable node and was freely movable.
Hashimoto's thyroiditis and a presumptive diagnosis of ST was made despite the subtleness of the history and clinical findings. Thyroid function

and inflammatory parameters resulted normal. Due to the lesion's suspicious features US guided FNA was requested. An asymmetric gland with a heterogeneous hypoechoic right lobe without individualized nodules was the only finding (11.2019).
Conclusion
ST is usually diagnosed clinically but the history/symptoms may be heterogenous, vague and the characteristic triphasic pattern of TFT may not be identified. US characteristics are focal heterogenous (markedly) hypoechoic areas of irregular and hill-defined borders. Lesions may be taller-than-wide and oedematous disruption of the perithyroidal capsular echogenic line may suggest extrathyroidal extension. Lack of microcalcifications or suspicious ganglia and a centripetal reduction in echogenicity have been reported to be the most distinctive features for ST. FNA may pose challenges to the cytopathologist and follow up US (after 2–5 months) may indetify resolution. In doubtful scenarios deliberation between FNA vs follow-up US may be considered to document normalization of echogenicity and uncover any suspicious thyroid nodules obscured by the inflammatory changes.

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EP507

What is responsible for subacute thyroiditis? Virus or immune system: A case report

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Background
Subacute thyroiditis (SAT) is a transient thyrotoxic state characterized by suppressed TSH and low uptake of iodine 123 on thyroid scanning. SAT is a self limiting, possibly viral and inflammatory thyroid disorder that is usually associated with thyroid pain and systemic symptoms. Many factors can cause SAT. Infections are considered the most common cause. Vaccines can also lead to SAT.
Case report
A 46-year-old male with a history of type 1 diabetes mellitus admitted to the hospital with fatigue, weight loss, myalgia and mild anterior neck pain. In November 2019, about four weeks before admission to our hospital, the patient received the seasonal influenza vaccine [VaxigripTetra- Quadrivalent influenza vaccine; batch number T3J232V, Sanofi Pasteur, Val de Reuil, France, containing the following strains: A/Brisbane/02/2018 (H1N1) pdm09; A/Kansas/14/2017 (H3N2); B/Colorado/06/2017; and B/Phuket/3073/2013], and at the time of vaccination, there was no prior history of thyroid disease or symptoms to suggest a recent viral infection. However, one week following the vaccination, the patient developed fever, sore throat, fatigue, myalgia and muscle weakness. He received antibiotherapy for two weeks. The patient had no symptoms or physical examination findings of upper respiratory system infection, and he had no obvious fever at the time of admission to the hospital. His heart rate was 112/min and regular. He had tenderness in both thyroid lobes. His laboratory tests showed a white blood cell (WBC) count of 9.12/µl (normal, 4.6–10.2), His kidney and liver functions were normal. Tests for thyroid autoimmune antibodies (thyroperoxidase and thyroglobulin) were negative. Ultrasonographic imaging and thyroid scintigraphy confirmed diagnosis of SAT. The table presents the time-varying laboratory parameters at admission and after steroid treatment (Table 1). The patient was started on 32 mg/day oral methylprednisolone treatment. His symptoms improved with treatment. With the two-month treatment period, the steroid dose was gradually reduced and discontinued. The patient asymptomatic in the third month of follow-up.

Table 1 Laboratory parameters following influenza vaccine.

	4. week	7. week	9. week	15.week	Referance range
TSH	0.01	4.15	10.08	5.82	0.5–5.5 mIU/l
FT4	2.17	0.78	1.09	1.22	0.89–1.76 ng/ml
FT3	4.81	1.94	2.67	3.25	2.3–4.2 pmol/l
ESR	21	9	5	3	0–15 mm/h
CRP	<0.34	0.02	<0.34	<0.34	0–0.5 mg/dl

TSH; thyroid-stimulating hormone, FT4; free thyroxine, FT3; free triiodothyronine,
ESR; erythrocyte sedimentation rate, CRP; C reactive protein

Conclusion
SAT should be suspected if influenza-like symptoms and pain in the thyroid region develop after influenza vaccination.

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EP508

The place of radioactive iodine remnant ablation in papillary thyroid microcarcinoma

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Introduction
Thyroid papillary microcarcinoma is a subtype of papillary carcinoma that included tumors with less than 10 mm diameter. Its therapeutic management is still a subject of controversy.
Material and methods
We conducted a retrospective study over 20 cases of papillary thyroid microcarcinoma at the ENT department of Tahar Sfar Hospital in Mahdia over 17 years (2000–2017).
Results
We report 20 cases of papillary thyroid microcarcinoma occuring in 18 women and 2 men. The mean age was 42 years ranging from 24 years to 75 years. A family history of thyroid pathology was noted in three cases and no prior history of cervical radiation or thyroid surgery was found. The ultra sound of the neck showed benign thyroid nodules in 18 cases and lateral lymph node associated to a suspect infracentimetric nodule in two cases. Lymph node metastases of papillary carcinoma were detected by fine needle aspiration cytology in these two cases. Total thyroidectomy was performed for 8 cases of multinodular goiters, thyroid lobectomy for 10 cases of a thyroid nodule. The intra operative pathologic examination was benign for these cases. Total thyroidectomy associated to central and lateral lymph node dissection was undergone in two cases. All the cases of thyroid microcacinoma were found during final pathologic examination. Lymph node metastases were noted in nine cases. Completion thyroidectomy following lobectomy that was associated to a central lymph node dissection was performed for 8 cases. Two cases of lobectomy did not perform this procedure since the size of microcacinoma was successively 1 and 2 mm. Radio-active Iodine remnant ablation treatment was indicated in 15 patients: 9 cases of lymph node metastases, extra thyroidal invasion in 5 cases and bilateral microcarcinoma in one case. A six years mean follow-up revealed no recurrence or death.
Conclusion
Papillary thyroid microcarcinoma have favourable long-term prognosis. Its management is multidisciplinary. A controversy exists regarding the role of radioactive iodine remnant ablation in this type of tumor. The indication of it depends on histological data.

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EP509

Chronic lymphocytic thyroiditis

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Introduction
Chronic lymphocytic thyroiditis is an autoimmune pathology affecting 5% of the population. Treatment is most often medical based on hormone treatment. Sometimes thyroiditis will be associated with benign or malignant nodular pathologies requiring the use of surgery. The objective of this study is to describe the diagnostic, therapeutic and evolutionary features of this entity.
Materials and methods
It is a retrospective study bringing 28 cases of chronic lymphocytic thyroiditis collected over a period of 15 years.
Results
The average age of our patients was 44 years (23 to 70 years) with a clear female predominance (26 women and 2 men). Anterior cervical swelling was the reason for consultation in all cases, associated with dysphagia in 4 patients and dyspnea in 2 patients. Cervical ultrasound, performed in all patients revealed a multinodular goiter in 53% of the cases, an isolated nodule

in 42% of the cases and an appearance of thyroiditis in 0.3% of the cases. Thyroid scintigraphy performed in 3 patients, objectified a hetero-nodular goiter in 9 cases and a cold nodule in 4 cases. Hypothyroidism was noted in 6 patients. All the patients were operated, having had a lobo-isthmectomy in 36% of the cases and a total thyroidectomy in 64% of the cases. The final histological examination showed Hashimoto thyroiditis in 14 patients, lymphocytic thyroiditis associated with an adenoma in 8 patients, a multinodular goiter in 4 patients, a papillary carcinoma in one case and a lymphoma in one case.
Conclusion
The frequency of the lymphocytic thyroiditis association with a multinodular goiter, an adenoma, a thyroid cancer has prompted several etiopathogenic studies in order to clarify the peculiarities of this coexistence.

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EP510

Case report of a very unusual thyroid nodule

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Background
Branchial cleft cysts account for almost 20 percent of pediatric neck masses. They are usually present in late childhood or early adulthood, when a previously unrecognized cyst becomes infected. First branchial cleft cysts typically appear on the face near the auricle. Second branchial cleft cysts are the most common and they are usually located just inferior to the angle of the mandible and anterior to the sternocleidomastoid muscle. Third branchial cleft cysts are typically located lower in the neck than the second one. First step in management is controlling infection, if present. Once the infection has been resolved, the mass is usually excised to prevent future complications.
Case presentation
A 72-year-old man was incidentally found to have a nodule in left thyroid lobule (LTL) during the performance of a carotid doppler ultrasound. The patient had personal history of transient ischemic attack in 2016, type 2 diabetes, dyslipidemia, arterial hypertension, Wolf-Parkinson-White syndrome and prostate carcinoma (in remission). He followed treatment with aspirin, metformin, atorvastatin and ramipril). There was no family history of thyroid carcinoma. Palpation of the neck was normal. He presented normal thyroid hormone levels with positive autoimmunity. Thyroid ultrasound reported a normal size gland with 2 hyperechoic micronodules without suspicions characteristics in right lobule and one solid nodule (13 mm, markedly hypoechoic, heterogeneous with lobulated surroundings) in LTL, suggesting a malignant nodule (TIRADS4c). Ultrasound guided fine-needle aspiration cytology was performed, which revealed four times insufficient specimen (Bethesda I) describing: protein hemorrhagic background with abundant anucleated cytoplasms and mature flat pavement cells, as well as crystalline deposits, without thyroid elements or with 3–4 follicular groups insufficient for diagnosis. With these results, a left hemithyroidectomy was performed.
Examination of the pathology sample reported an intrathyroidal branchial cleft cyst with collapsed light, microscopically, presented occasional anucleated laminates and cellular detritus, which were coated by squamosian epithelium without grain, lacking of atypia. Also, an incidental 1 mm papillary carcinoma was found, with free resection margins.
Conclusion
This report represents a rare case of branchial cleft cyst because of the location and the age of our patient. The literature review reveals the existence of only 6 cases of intrathyroidal branchial cleft cyst. There are not specific ultrasound or cytology characteristics, resulting in the need for surgery to reach a diagnosis.

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EP511

Concurrent central diabetes insipitus and thyroid hormone resistance syndrome

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A 47-year-old male farmer presented to our endocrinology clinic in 2001 with progressive polyuria for half a year. He had a past history of left intracranial hemorrhage with right hemiparesis due to traumatic injury in November 1998 but recovered thereafter. He complained of urine output more than 10 000 c.c. per day. Routine urine check with SP. GRAVITY < 1.005 was noted (Normal range: 1.005–1.030). Serum osmolality was 299 mosm/KgH_2O (Normal range: 275–295) while urine osmolality was 86 mosm/KgH_2O (Normal range: 50–1400). We also checked his serum ADH level which was 0.13 pg/ml (Normal range: 0.4–2.4), and therefore central diabetes insipidus (DI) was impressed. In addition, serum level of pituitary hormones, including luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, growth hormone (GH), adrenocorticotropic hormone (ACTH) were normal. However, elevated serum FT4 level (FT4: 2.22 ng/dl) (Normal range: 0.85–1.86 ng/dl) with higher serum TSH level (TSH 13.7 ulU/ml) (Normal range: 0.25–4 ulU/ml) was noted. Serum TBII level was 4.45% (Normal < 15%). Repeated thyroid function test revealed similar results with slightly higher serum FT4 level and normal to higher serum TSH level. Brain magnetic resonance imaging (MRI) was performed and revealed no pituitary mass. The patient did not have any symptoms and signs of hyperthyroidism, such as weight loss, heat intolerance, hand tremor and tachycardia. Thyroid ultrasonography was performed and showed a normal thyroid. Thus, thyroid hormone resistance syndrome was suspected. Except a large amount of DDAVP (nasal spray) (10 mg/ds, 25 ds/bot) 5 bottles per months, he did not receive any treatment for abnormal thyroid function. Serum FT4 level has been continued to be higher than normal with a normal to higher serum TSH level. In conclusion, our patient had been diagnosed with central diabetes insipitus and thyroid hormone resistance syndrome.

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EP512

A rare complication of thyrotoxicosis: diabetic ketoacidosis

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Graves' disease is the most common cause of hyperthyroidism. It is well established that hyperthyroidism promotes a hypermetabolic state characterized by increased resting energy expenditure, increased lipolysis and gluconeogenesis. We describe a rare complication of thyrotoxicosis in a patient with type II diabetes on insulin, with no previous thyroid history. An 83 year old woman with type 2 diabetes on biphasic insulin presented with symptoms of polyuria, polydipsia and fatigue. She was tachycardic and tachypneic but normotensive and apyrexial with no obvious focus of infection. Her clinical examination revealed no abnormalities and initial investigations showed blood glucose of 26 mmol/l, ketones 4.8 mmol/l, pH 7.19 and bicarbonate of 14 mmol/l confirming diagnosis of Diabetic Keto-Acidosis (DKA). A thyroid function panel was ordered which showed her thyroid stimulating hormone was < 0.003 with a free T4 level of 64.1 mg/l. A diagnosis of Graves' disease was made based upon her positive thyroid stimulating hormone receptor antibody (TSH-R). The patient improved upon starting management for DKA with resultant closure of anion gap and resolution of DKA. Treatment for thyrotoxicosis was also initiated with propranolol and carbimazole to manage her thyroid state with good response. She was discharged on biphasic insulin and newly commenced on anti-thyroid medication. Our case emphasizes that inadequately treated thyroid disease can negatively impact diabetes control. Increased glucose uptake and increased insulin clearance in hyperthyroidism creates a relative insulinopenic state that can manifest as DKA. Graves' thyroid patients with diabetes can have suboptimal blood sugar control in hyperthyroid state and they should be warned about DKA as a potential complication.

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EP513

Graves' disease and papillary thyroid cancer: Clinical case

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Background
Graves' disease in combination with thyroid nodules is more common in women. However, more than one in three patients has carcinoma.

Unfortunately, thyroid cancer is most frequently detected accidentally after a thyroidectomy for Graves' disease, despite the wide possibilities of modern diagnostic methods.
Clinical case
A 55-year women complained of discomfort in the neck, sweating, irritability, palpitation. From anamnesis: in 2012 she was diagnosed with thyrotoxicosis syndrome. For 5 years, the patient was treated with thyrostatics, but when trying to reduce the dose, the syndrome of thyrotoxicosis recurred. In March 2017, the patient's condition worsened, at the time of treatment she took Thyrosol 30 mg/day.
Objectively
Hypersthenic body type, BMI 33 kg/m^2. Thyroid gland visually was increased in volume, dense with palpation, homogeneous, mobile. Elevated titer of antibodies to the TSH receptor was discovered, according to the ultrasound – increase thyroid gland 30.2 cm^3, hyperechogenic formation of the left lobe 10×10×9 mm with hypoechoic rim, clear smooth contours, intranodular blood flow. As a result, the Graves' disease, goiter grade 2, manifest thyrotoxicosis was verified, surgical treatment was recommended. Thyroidectomy, histological examination was performed: Graves' disease was confirmed, papillary microcarcinoma with metastasis to 1 regional lymph node was revealed. Diagnosed: papillary thyroid cancer I st (pT1aN1aM0x), 2 clinical group. The patient was prescribed suppressive therapy with L-thyroxine 100 μg/day, against which after 3 months TSH reached the target values (0.2–0.5 Mme/l). Taking into account the histological characteristics of the tumor, the nature and volume of the lesion, age, the patient belongs to the group of intermediate cancer risk of progression of cancer. According to scintigraphy residual functioning thyroid tissue (20 × 15 mm) was detected. Radioiodine therapy was carried out in a specialized hospital. Suppressive therapy of L-thyroxine 150 μg/day, target values of TSH 0.1–0.5 Mme/l was recommended. After 6 months, TSH reached target values, and according to the results of ultrasound of thyroid gland no data for structural relapse was found.
Conclusion
Long-term recurrent Graves' disease with a dubious effect of conservative therapy, in the presence of nodular formation, should alert the doctor to the presence of thyroid cancer. Such patients are needed in carefully examination, as necessity for surgery should be determined.

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EP514

Management and evolution of papillary thyroid carcinoma in a patient with acromegaly

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Background
Acromegaly is a chronic rare disease induced by persistent hypersecretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) in adult patients. Several studies have associated acromegaly with an increased risk for developing different benign or malignant tumors.
Case presentation
A 33-year old female patient was diagnosed with acromegaly due to a large pituitary macroadenoma, in 2009. In the same period, she was also diagnosed with a very large and compressive nodular goiter with retrosternal extension and underwent a subtotal thyroidectomy. The pathological exam established that it was a papillary thyroid carcinoma (PTC). Therefore, two further surgeries were performed for the complete removal of the thyroid tissue. The pituitary adenoma was treated 6 months later through endoscopic transsphenoidal surgery, but a residual tumor mass remained in the left cavernous sinus, that was managed by external radiotherapy, followed by the administration of Somatostatin analogues (SMA) for six years. The patient developed thyrotropic and gonadotropic insufficiency after the neurosurgical intervention. Radioiodine therapy was necessary for thyroid carcinoma, but the administration of Thyrogen was mandatory due to the suppressed TSH induced by pituitary insufficiency. The evolution of the case was favorable under therapy and the patient is now in a satisfactory condition, with a good quality of life. The Thyroglobulin level is undetectable (0.04 ng/dl) and the last IGF-1 value, four months after discontinuation SMA, was normal (103, NV 58–219 ng/ml).
Discussion
This case present one patient from our acromegalic series, who was detected with PTC in the moment of diagnosis. Many studies reported a high prevalence of thyroid cancer, between 1.2–11% among acromegalic patients. Sustained exposure to high serum IGF-1 levels seems likely to play a role in the development of the malignant disease, by stimulating the proliferation of different cells and by inducing an antiapoptotic effect on thyroid follicular cells. Some studies suggested a role for different factors like pituitary radiotherapy, obesity, insulin resistance, IGF-binding proteins, in development of thyroid cancer.
The diagnosis and the management of this case were difficult and challenging, but the evolution of this case was favorable, with cure of diseases, PTC and acromegaly.
Conclusion
A careful evaluation and management allow a favorable evolution in this case. Patients with acromegaly should be routinely screened for thyroid pathology at first evaluation, to allow an earlier detection of associated thyroid disease.

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EP515

Grave's disease as a rare cause of pericardial effusion

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Introduction
The auto immune's diseases are also involved in the heart's failure. Grave disease(GD) is an autoimmune thyroid disease that often linked by pericarditis. We report a case of an acute pericarditis that was also presumed to be associated with GD.
Case report
A 59 years old who 10 pack years smoker. admitted for chest pain and shortness breathstage 3NYHA. At the investigation there was a progessive emaciation of 12 kg within 7 months with palpitations and repeated diarrhea. 4 days ago he presented a progressive setting dyspnea with orthopnea with intense chest pain. At the examination, skinny patient, radiance to the eye. There was a homogeneous thyroid enlargement with thrill and neck vein engorgement. There was no foot 's oedema,pulse rate of 109 beats per minute and a normal blood pression at 120/80 The heartbeat was regular and no cardiac murmur including precordial friction rub could be identified. Laboratory results showed a stunted TSH at 0,005 μg/ml( ), T4L: 70 pmol/l(12–22), a neck echography hypervascularized with a homogeneous goiter, the thyroid's antibody were positive by anti RTSh on 38(*N*<1.75). Transthoracic echocardiography showed circumferential effusion with hemodynamic consequences. The blood count and liver's enzymes were normal and the remaining part of the immunologic and serology is featureless. The management consisted in 3 pericardial drainage and etiological treatment under ATS in offensive trend of 60 mg of carbimazole, propranolol 40 mg ½ cp*3/d.
The favorable development with the pericardium drying and clinic stabilization and biological and hyperthyroidicism.
Discussion
The pericarditis with effusion in GD can happen by autoimmune mechanism involving a direct or indirect interaction between the Ac anti receptor and the pericardium. The thyrotoxicosis affects the metabolism of the pericardial's brown fat. The well taken ATS treatment must be completed by a radical treatment because of the high recidivism risk. The ATS choice is crucial because of pericarditis drug risk due to PTU.
Conclusion
The etiology research to a pericarditis must always involve a thyroid check not just to a research of a hypothyroidism commonly associated but also a hyperthyroidism notably in more frequently form which is the GD.

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EP516

Treatment of hypothyroidism does not affect whole-body oxidative stress, as measured by biomarkers of RNA and DNA damage

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Background
Hyperthyroidism as well as hypothyroidism have been associated with oxidative stress, caused by an imbalance between pro-oxidants and anti-oxidants. Oxidative stress may damage the genomic apparatus and other cellular structures. Urinary excretion of 8-oxo-7.8-dihydroguanosine (8-oxoGuo) and 8-oxo-7.8-dihydro-2'-deoxyguanosine (8-oxodG), respectively, represent global RNA and DNA oxidation, thus reflecting oxidatively generated modification of nucleic acids in the entire organism. While these biomarkers have been associated with increased morbidity and mortality in various diseases, they have only sparsely been explored in patients with thyroid disorders.
Method
Twenty-eight hypothyroid women (overt: $n=6$; subclinical: $n=22$) were included in a prospective cohort study. Mean age was 48.4±10.8(s.d.) years at diagnosis. Urinary excretion of 8-oxoGuo and 8-oxodG, corrected for creatinine, were measured shortly after initiation of levothyroxine (LT4) supplementation [mean 38±26 days between start of treatment and first study visit], and after a minimum 12 months of stable euthyroidism.
Results
Before treatment, TSH was 9.40±4.97 mIU/l and total T4 was 75.0±18.4 nmol/l. Mean follow-up time was 604±251 days. When euthyroid, the mean LT4 dose was 112±36 μg, and TSH had decreased to 2.48±2.08 mIU/l. As 8-oxoGuo and 8-oxodG were not normally distributed, a logarithmic transformation was applied. Compared to baseline, none of the biomarkers changed significantly after 12 months of euthyroidism. 8-oxoGuo: geometric mean (GM) 1.82 (95% CI: 1.62–2.03) nmol/mmol creatinine at baseline and GM 1.88 nmol/mmol creatinine (95% CI: 1.67–2.11) at euthyroidism, $P=0.51$. 8-oxodG: GM 1.37 nmol/mmol creatinine (95% CI: 1.15–1.64) at baseline and GM 1.45 nmol/mmol creatinine (95% CI: 1.23–1.70) at euthyroidism, $P=0.44$.
Conclusions
To the best of our knowledge this is the first study to evaluate the impact of LT4 treatment in hypothyroid patients on the excretion of the nucleic acid metabolites 8-oxoGuo and 8-oxodG. We found no significant effect of restoration of euthyroidism on these biomarkers of whole-body oxidative stress. However, the negative finding may be explained by most of our patients having subclinical rather than overt hypothyroidism. Thus, larger studies of patients with more severe thyroid failure are needed to further explore the relationship between hypothyroidism, its treatment, and whole-body oxidative stress.

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EP517

Frequency of circulating antithyroid antibodies among the patients with thyroid diseases

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Background
Increasing of the level of circulating Antithyroid autoantibodies suggested about autoimmune destruction in thyroid gland and not always depends from thyroid status. We aimed to study the frequency of circulating antithyroid autoantibodies (ATAB) in people with the different thyroid diseases.
Material and methods
In 25 people with high level of circulating ATAB blood serum TSH, T3, T4, glucose, ALAT, protein, albumin levels were measured. Thyroid gland ultrasound and ECG were performed. HR and BP were assessed.
Results
According to thyroid function in 64% were determined euthyreosis (TSH 1.6 ng/ml), in 24% with hyperthyroidism (TSH 0.1 ng/ml) and 12% with hypothyroidism (TSH 15.4 ng/ml). The average levels of ATAB were comparable between the groups and were four times higher than in healthy subjects. There were no significant differences in blood Calcium, Phosphorus level and alkaline phosphatase activity, whereas blood total protein, albumin, ALAT levels were oppositely linked with thyroid function. Interestingly, higher level of ATAB were accompanied with impaired glycemia in 56% patients with ecthyreosis, in 17% with hyperthyrosis and no glycemia impairments were detected in patients with hypothyreosis.
Conclusion
In patients with higher circulating ATAB mostly detected euthyreosis (in 64%) than hyperthyreosis (in 24%) and hypothyreosis (in 12%). In people with higher ATAB the glycemia impairments were determined in those with euthyreosis (56%) and hyperthyreosis (17%).

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EP518

Management of subclinical hyperthyroidism presented by several cases

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Subclinical hyperthyroidism (ScHyper) is a condition with suppressed TSH, and normal free T3 and free T4 hormones, affecting 10% of the population. There are two subgroups of patients, the first group with TSH lower than 0.1 U/l, and the second group with mildly suppressed TSH between 0.1 and the lower assay reference limit. The patients from the first group should be treated, but there is no evidence for therapy for the second group of patients. We present a three cases from the second group of patients with ScHyper and their different management of the disease. The pregnant women in the first trimester of pregnancy wasn't treated, just observed. The TSH spontaneously normalized in the second trimester of pregnancy. Patient with ScHyper caused by Graves' disease was treated only with beta blocker because of tachycardia. And, older women with multinodular goiter, who refused iodine 131 therapy, was treated with low doses of antithyroid drug and beta blocker. All three were without any complications from the disease. Treatment options of ScHyper are: antithyroid drugs, iodine 131 therapy, and surgery. Which of these will be chosen, or patient will be observed without therapy, depends to the specific causes.
Keywords: subclinical hyperthyroidism, Graves' disease, TSH reference values.

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EP519

The Role of Selenium and Iodine on thyroid status in the first trimester of pregnancy

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Introduction
Pregnant women are at risk for selenium deficiency, which is known to maintain adequate function of immune system and thyroprotective enzymes. Same, iodine is an essential micronutrient for thyroid hormone synthesis and important endocrine regulator of early brain development. Our previous study revealed that 81% of pregnant women in Latvia have insufficient levels of iodine. The aim of the present study was to evaluate iodine and selenium supply during pregnancy in recent years, and to analyze its association with thyroid function and autoimmunity.
Methods
123 pregnant women during the first trimester were included in a cross-sectional study in 2017–2019. Urinary iodine concentration(UIC) was

measured using the ammonium-persulfate method. Thyroid status was assessed by measuring thyroid stimulating hormone(TSH), free T4(FT4), thyroid peroxidase antibodies(TPO-ab). Serum selenium level was detected in 111 participants.
Results
Out of 123 participants(age 29.23±4.568;(min 17; max 40)) 65(52.8%) had UIC below the WHO recommended level of ≥150 μg/g during the first trimester of pregnancy. Furthermore, 34 patients(27.6%) were iodine deficient (UIC<100 μg/g). The median UIC was 147.21 μg/g Cr(IQR 89.99–248.1), which is regarded as suboptimal. There was no statistically significant correlation between UIC and TSH (0.047; $P=0.618$), FT4 (–-0.028; $P=0.769$) or TPO-ab (0.012; $P=0.895$). In addition, suboptimal iodine status did not have significant impact on thyroid function, as median TSH was 1.1 (IQR 0.676–1.45) mU/l in patients with suboptimal UIC(Group 1) and 1.0 (IQR 0.7–1.5) in patients with sufficient levels of UIC(Group 2), $P=0.816$. Mean FT4 was not affected either: group 1 mean FT4–14.2 pmol/l (95% CI 13.36–15.03) and 14.14 pmol/l(95% CI 13.62–14.65) in Group 2 ($P=0.911$). Moreover, it had no effect on TPO-ab levels: 28 (95% CI 27–40) vs 27 (95%CI 27–39, $P=0.612$). The mean serum selenium concentration was 102.07±37.01 μg/l (min 26.5; max 212.31). Furthermore, selenium concentration showed a statistically non-significant tendency of negative correlation with TPO-ab(0.027, $P=0.783$) and TSH(–0.120, $P=0.217$). 15 participants with increased TPO-ab(> 60) were characterized by lower levels of selenium as compared to those 93 with normal TPO-ab levels (≤ 60): 91.15(95% CI 71.07–111.23) vs. 103.10 μg/l (95% CI 95.62–110.58). There was no impact of selenium status on mean FT4(0.0, $P=0.996$).
Conclusions
More than half of pregnant women had UIC below the WHO recommended level of adequate iodine supply. However, mean serum selenium level was detected to be sufficient in the first trimester of pregnancy. Yet a negative correlation between TSH, TPO-ab and serum selenium levels was found. There was no significant association between UIC, selenium status and thyroid function.
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Magnitude of increase in levothyroxine requirements during pregnancy in women with pregestational hypothyroidism in navarra (Spain)
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Introduction
Hypothyroidism during pregnancy has been asociated with adverse maternal and neonatal outcomes. During pregnancy, maternal levothyroxine (LT4) dose requirements increase. The aim of this study is to determine the increase of LT4 doses during pregnancy in pregestational hypothyroid women.
Methods
We included 76 hypothyroid pregnant women. We analyzed analytical and clinical characteristics of these patients, as well as the increase of LT4 requirement during pregnancy. We used the statistical software SPSS version 20.
RESULTS
Fifty-two women had autoimmune hypothyroidism (68.4%). The mean prepregnancy TSH was 2.46±1.25 mU/l and the prepregnancy LT4 requeriment was 75.3±32.3 μg/d. An increase in the LT4 dose was necessary in 64 women (84.2%). The mean LT4 requirement increased 44±45 percent. Women with LT4≤50 μg/d increased LT4 by 63%, those between 51–100 μg/d and>100 μg/d increased by 33% and 25% respectively ($P=0.008$). Women with higher levels of anti-Tg antibodies required a higher LT4 dose (70% vs. 37%, $P=0.025$). There is also a higher dose increase in women with prepregnancy TSH>2.5 mU/l, but these differences were not statistically significant.
Conclusion
Most pregestational hypothyroid women require an increase in daily substitutive doses of LT4 during pregnancy. The mean LT4 requirement increased 45% percent during pregnancy. Women with lower prepregnancy LT4 requirement and women with higher levels of anti-Tg antibodies needed a higher dose increase.
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EP521

Radioiodine therapy and Graves' disease
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Used for the first time in 1941 in the United States by Hertz and Roberts for the treatment of hyperthyroidism in Grave's Disease, radioactive active therapy (RAI) has been able to gain its place within the already existing therapeutic arsenal by being efficient, easy to use and minimally invasive. Our work is a retrospective study of 46 patients collected at the Department of Endocrinology, over a period of 7 years and half from January 1, 2011 to June 30, 2018. The purpose of this study is to determine the place of radioiodine therapy in the treatment of Graves' disease in our context, and to evaluate its results. We defined 2 groups of patients: An 'A' group corresponding to all 46 patients followed for Graves' disease (the average age was 43 years and the sex ratio (F/M) was 0.84), including a subgroup 'B' corresponding to the 17 patients treated with RAI (the average age is 41 years and the sex ratio (F/M) was 1.12). All patients in group 'A' received first-line medical treatment, 37% of whom resorted to RAI because of either resistance to treatment in 70.6% of cases, relapse in 23.5% of cases, or serious side effects (severe leukoneutropenia and cholestatic hepatitis) caused by antithyroid drugs (ATD) which required an immediate interruption of the treatment in 5.9% of cases. Thirteen patients in group 'B' received a single dose of radioiodine (76.5%), 3 patients received 2 doses (17.6%) and only 1 patient received 3 doses of treatment (5.9%). The administered activities were between 8 and 15 mCi. The average activity administered in the first dose of treatment was 9.7 mCi (41.2% received 8 mCi, 52.9% received an activity between 10 and 12 mCi and 5.9% received an activity>12 mCi). The average activity of the 2nd dose of treatment was 9.2 mCi. The additional doses were justified by either resistance to ATDs or persistence of hyperthyroidism. The administration of iodine was very well tolerated. Only one case of xerophthalmia and ocular pain was noted in the short term.
The long-term results were as follows:
– 29.4% benefited from a return to euthyroidism.
– 47.1% went into hypothyroidism.
– 23.5% are still hyperthyroid.
Overall, the treatment was successful in 76.5% of cases and failed in 23.5% of cases. Despite the limited number of patients and the short period we had in order to evaluate this therapy, the results seem encouraging.
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Autoimmune polyglandular syndrome type 3
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Introduction
Autoimmune polyendocrine syndrome (APS) is a rare, inherited disorder, characterized by autoimmune thyroiditis with another organ specific autoimmune disease.
Observation
We report the case of 55 years old woman, descendant of a first degree consanguineous marriage, who presented at the age of 35 a premature ovarian insufficiency and alopecia. Eight months later, she developed a goiter with hyperthyroidism and the diagnosis of Grave's disease was confirmed in front of high level of anti TSH receptor antibodies. During her hospitalization, we discovered a pancytopenia with severe anemia that needed a transfusion. Then she presented a diarrhea and the diagnosis of coeliac disease was confirmed. The procedure to follow was to put the patient under gluten free diet, and she was treated for her Grave's disease with radioactive iodine. This patient present an autoimmune polyglandular syndrome type 3C which is the association of autoimmune thyroiditis with alopecia and other organ-specific autoimmune disease.
Conclusion
APS is an autoimmune condition that affects the body's endocrine glands, the cause is still unknown. Type three is more often seen in women in middle age. The morbi-mortality is determined by the specifics of each syndrome. It is important to assure the follow up of the patients to detect and diagnose the other autoimmunes disorders at an early stage.
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EP523

Low TSH level and twin pregnancy. A case report

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Introduction
Thyroid physiology changes during pregnancy so the use of pregnancy-specific reference ranges for TSH and FT4 in order to adequately diagnose gestational thyroid disease is necessary. According to literature, in twin pregnancy, TSH can be in low levels during first trimester due to a much higher and more sustained peak of hCG (TSH-like activity of human chorionic gonadotropin) but it will be normalized at the end of the second trimester or within 22 weeks. Hyperemesis gravidarum (HG) is reported to occur in 0.3% to 1.0% of pregnancies.
Case report
Our patient, Caucasian female, 42 years old, pregnant 22 weeks, hospitalized at maternity hospital for being under close medical care. Before current pregnancy she had had 5 abortions (2 natural pregnancies and 3 pregnancies under IVF treatment). The current pregnancy has also been assisted by in vitro fertilization techniques. During the first 16 weeks of pregnancy she had been having hyperemesis gravidarum. In following she was without nausea and vomitus. She complained anorexia and fatigue. Familiar history and her life history not related to thyroid disease. She had normal weight body, mild hands tremor, and palpitations with a pulse rate of 100 beats per minute. Laboratory examinations reveled a TSH 0.006 IU/l. She was evaluated for thyroid diseases. FT4=14.2 pg/ml (7–18), FT3=3.9 pg/ml (2–4.25), T4 11.2 μg/ml (5.1–14.1) R-TSH ac 0.37UI/ml (<1). Thyroid ultrasound resulted normal. She was followed by repeating TSH, T3, T4 every month until delivering. It was noted that TSH stood in low levels (0.001 Ulu/ml) until delivering but FT4 and T4 in normal value. She was very stressed during her pregnancy because of fear of losing the pregnancy again. She underwent section cesarean at 35 weeks and she gave birth a healthy male child 2000 gr and a hypotrophy female child 1400 gr.
Conclusion
Every medical physician who takes care of a twin pregnancy, must recognize that a TSH level that keeps standing quite low (more than 22 weeks of pregnancy), does not always correspond with thyroid dysfunction and may be caused by other conditions such as hyperemesis gravidarum, higher level of hCG during twin gestation than pregnancy with a baby and maternal chronic stress. We thought that a combination of all these conditions have kept quite low TSH level until the end of pregnancy.

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Oncological disease mimicking endocrine pathology – a challenging case report

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Introduction
Patient with co existing oncological disease can easily be misunderstood by endocrinological pathology as hypothyroid, both representing similar appearances. The aim of this case report is to stress the importance of multidisciplinary teamwork, meaning of follow up, and increase knowledge about side effects of hormonal therapy which could affect endocrine system.
Case report
A patient 55 years old female complaining about weakness, dry skin, hair loss, constipation and headaches was referred to general practitioner and by examining autoimmune thyroiditis with elevated TSH-11 mU/l and anti TPO – 900 IU/ml, low fT4–7 pmol/l were found and Levothyroxine 25 mg OD was started. Few months after euthyroid state was reached, patient was diagnosed with infiltrative (Grade 2) ductal carcinoma (HER2 – positive) and left mammary gland sectoral resection with sentinel node biopsy was performed shortly afterwards. After the surgery surgeon and immunologist relying to a year-old lab results cancelled therapy of Levothyroxine, calling it useless. Chemotherapy by EC-T scheme, including Epirubicin 140 mg, Cyclophosphamide 1000 mg and Paclitaxel 300 mg was started with continuous hormonal therapy including Trastuzumab 600 mg by scheme and Tamoxifen 20 mg OD. Nine months after cancellation of thyroid hormone therapy patient with recurrent complaints about weakness was examined and high TSH – 25 mU/l, low normal fT4–12.4 pmol/l and clinically significant dyslipidemia (total cholesterol 6.45 mmol/l (< 5.0); LDL 3.88 mmol/l (< 3.0); Non HDL – 4.95 mmol/l (< 3.4); triglycerides – 3.37 mmol/l (< 2.0)) was found. Head MRI revealed multiple vascular lesions with hemosiderin deposition in basal ganglia. Initiation of Levothyroxine 25 mg OD followed, as well as continuation with Trastuzumab 600 mg by scheme and Tamoxifen 20 mg OD. Patient is now followed up by multidisciplinary team including endocrinologist and oncologist.
Conclusions
This case report reveals lack of multidisciplinary teamwork in patients with oncological disease receiving hormonal therapy, as well as treatment options in patients with subclinical thyroiditis causing severe dyslipidemia and importance of consideration of screening imaging of the brain for patients with HER2-positive subtypes.

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Continuous enteral feeding in a extremely refractory dumping syndrome

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Introduction
Dumping syndrome is a phenomenon produced by the alteration of the pyloric sphincter. It occurs in 20% of pyloroplasty or distal gastrectomies. The syndrome is attributed to the rapid emptying of the chyme in the intestine. The osmotic gradient attracts fluid to the intestine, and this releases vasoactive hormones, such as serotonin or vasoactive intestinal polypeptide.
Case report
We present a 82-year-old woman with gastric intervention in 1985 with pyloroplasty and vagotomy with early and late dumping syndrome. This situation was refractory to nutritional and medical treatment conditioning with frequent and severe hypoglycemia events. A hypoglycemia study was performed with a fasting test, anti-insulin antibodies and C-peptide that were normal. The possibility of home parenteral nutrition was ruled out because of the risk of infection and also surgical intervention because her comorbidities. The placement of a nasoyejunal catheter was chosen. Given the good tolerance it was decided to perform a radiological yejunostomy to definitely avoid hypoglycemia.
Discussion
Dumping syndrome is defined by a group of symptoms caused by rapid emptying of nutrients from the stomach into the small intestine. First line of the treatment includes dietary modifications. A small group of patients may require medical therapy with acarbose or octreotide. Nevertheless is extremely rare the use of continuous enteral feeding to avoid hypoglycemia symptoms.
Ethical aspects
The case has the informed consent of the patient.

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Central hypothyroidism secondary to oxcarbazepine therapy in children-a clinical case report

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Introduction
The change in thyroid parameters is described in the case of antiepileptic treatment in the pediatric population, due to interferences within the hypothalamo-pituitary-thyroid axis and due to the increase in the rate of hepatic metabolism of thyroid hormones.

Case presentation
We present the case of a 10-year-old boy who addressed our outpatient pediatric endocrinology department for endocrine evaluation in the context of weight growth about 10 kilograms, dry skin, poor growth velocity and low school performance, that developed progressively over the last 3 months. The patient associated a history of partial seizures and motor tics controlled with treatment with oxcarbazepine 900 miligrams per day for 1 year. The parents denied daily administration of biotin, corticosteroids, etc. On physical examination the child was overweight (87 percentile body mass index), had a normal height for his age (+0.16 s.d.) without active stretch marks, without hirsutism and with Tanner I prepubertal status.
Thyroid hormone profile indicated central hypothyroidism with low levels of thyroid stimulating hormone of 0.56 microUi/ml (normal range 0.6–4.5 microUi/ml) and decreased values for free thyroxine (FT4) and free triiodothyronine(T3) of 0.82 pmol/l and 75 ng/dl (normal range 0.89–1.34 pmol/l, respectively 80–200 ng/dl). The patient had normal laboratory evaluation, including liver and kidney function, complete blood count, prolactin and cortisol levels. The thyroid ultrasound indicated a homogenous structure, normal dimensions of thyroid gland and a normal vascularization. The magnetic resonance of the brain and the hypothalamo-pituitary region was within normal limits. The patient was started on levothyroxine therapy and clinical symptoms have improved together with the increase of free thyroxine values.
Conclusions
In conclusion, we present the case of a patient diagnosed with central hypothyroidism associated with oxcarbazepine treatment, emphasizing that oxcarbazepine can interfere with thyroid hormones axis.
Keywords: central hypothyroidism, oxcarbazepine.
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EP527

Thyroid diseases and mastopathy
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Aim
To assess the thyroid and reproductive system status in 222 women with normal menstrual cycles.
Material and methods
Patients were referred for thyroid ultrasonography and concurrent breast ultrasonography. The 160 women were divided into two groups, based on the nature of the thyroid pathology.
Results
The 1st group included 90 women with autoimmune thyroiditis (AIT), the median age was 36.00 [25.00; 50.00] years, the 2nd group – 70 women with nodular goiter, median age was 37.00 [31.00; 45.00] years. Women with AIT showed inverse significant correlations between age and testosterone level ($\rho=-0.32$; $P<0.001$), age and DHEAS level ($\rho=-0.38$; $P=0.001$), as well as BMI and FT_4 ($\rho=-0.24$; $P=0.04$). Direct significant correlations were established between progesterone and estradiol levels ($\rho=0.30$; $P=0.01$), progesterone and FT_3 levels ($\rho=0.24$; $P=0.04$). Testosterone had a direct significant correlation with the FT_3 level ($\rho=0.24$; $P=0.04$). DHEAS level had a direct significant correlation with the TSH level ($\rho=0.33$; $P=0.004$). Prolactin levels also had a direct significant correlation with estradiol levels ($\rho=0.23$; $P<0.05$). Age had a direct significant correlation with BMI ($\rho=0.50$; $P=0.001$). In the group of women with nodular goiter, age had an inverse significant correlation with progesterone levels ($\rho=-0.37$; $P=0.002$); testosterone levels ($\rho=-0.39$; $P=0.002$) and DHEAS levels ($\rho=-0.47$; $P<0.001$). An inverse significant correlation was established between progesterone and FSH levels ($\rho=-0.32$; $P=0.01$). In this group, a direct correlation was established between age and prolactin level ($\rho=0.31$; $P=0.01$) and BMI ($\rho=0.53$; $P<0.001$). The progesterone and testosterone levels had a direct significant correlation ($\rho=0.36$; $P=0.004$).
Conclusion
The obtained results indicate that the presence of thyroid pathology can be considered as one of the risk factors for the development of mastopathy.
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EP528

Thyroid disorder in patients with spondylarthritis
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Background
The association between spondylarthritis and thyroid diseases is unclear. Few studies have examined this association and results remain unknown. We aimed to assess the frequency of thyroid disorders among patients with spondylarthritis.
Methods
We performed a cross-sectional study including 50 patients with spondyloarthritis (SA) diagnosed according to ASAS criteria. The disease activity was assessed using ASDAS Free Thyroxine(FT4) and thyroid stimulating-hormone (TSH) were measured for each patient.
Results
The mean average was 45.75±13.18 years. The sex-ratio was 3. Clinical phenotypes of SA were: ankylosing spondylarthritis (60%), psoriaticarthritis (22.5%), arthritis associated with inflammatory bowel disease (12.5%). The mean duration of the disease was 91.6±61.17 months. The mean C-reactive protein and erythrocyte sedimentation rate were 32.21±43.09 mg/l and 34.36±24.9 mmH1 respectively. The mean ASDAS-CRP and BASMI were 3.83±2.33 and 2.11±2.23. The mean FT4 and TSH levels were 12.23 and 1.89 respectively. There is no Correlation between ASDAS, BASMI, inflammatory markers, and Thyroid hormone (FT4 and TSH). Disorder of at least one thyroid function test (FT4 or TSH) was noted in 27.5% of cases ($n=11$). Among these patients: 10% of patients ($n=4$) had a central hypothyroidism(low FT4 level and normal TSH level), 2.5% of patients ($n=1$) had a subclinical hyperthyroidism (n ormal FT4 level and low TSH level), and 2.5% of patients ($n=1$) had acquired hyperthyroidism (high FT4 level and low TSH level). A normal TSH associated with high FT4 was found in 12.5% of ($n=5$). This finding may correspond to thyroid hormone resistance, an artifact or a thyrotropic microadenoma.
Conclusion
Our study showed that thyroid disorder is not uncommon in patients with SA. The main disorder observed in our study is a high free T4 associated with normal TSH level. Our study suggests that the screening of thyroid disorder is mandatory in patients with SA.
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Recurrent subacute thyroiditis associated with microscopic polyangiitis (ANCA positive vasculitis)
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A 56 year old lady was investigated by her GP for arthralgia and found to be thyrotoxic (TSH<0.01 mU/l, free T4 34.8 (10–20 pmol/l), TPO 50 (<35 IU/ml)). She gave a history of anterior uveitis some 20 years earlier. She was commenced on carbimazole and referred to the endocrinology clinic, where her thyroid function rapidly normalised and a biochemical diagnosis of subacute thyroiditis was made. Thyroid pertechnatate scan showed reduced uptake throughout the gland. TSH receptor antibodies were negative. It was noted she had had a similar episode 11 years earlier. Investigations for breathlessness revealed some ground glass appearances on CT. Two further episodes of thyroiditis occurred, each one asymptomatic. She was found to be MPO-ANCA positive, for which prednisolone and subsequently mycophenolate mofetil was commenced for a diagnosis of microscopic polyangiitis. Eleven years later she developed hypothyroidism, presumed following another episode of thyroiditis, and levothyroxine commenced with normalisation of thyroid function, and a plan for radioiodine treatment if further episodes occurred. Microscopic polyangiitis is a small vessel necrotising vasculitis typically affecting the lungs, kidneys, eyes and other vascular beds, and most commonly associated with MPO-ANCA positivity. The understanding of the relationship between the thyroid and vasculitis is evolving. It is well recognised that ANCA positivity (MPO, PR3 or both) can occur frequently with thiouracil derivates more often than MMI derivatives, and that 15% of

these patients can exhibit a clinical vasculitis, though presentation is heterogeneous. In addition, thyroid disease seems to occur more frequently in patients with vasculitis, perhaps up to 40% with ANCA positive vasculitis. Those of MPO positivity and female sex and are more likely, with the most common outcome being hypothyroidism. The link is not established, though theories include genetic predisposition, loss of tolerance to peroxidases and cross reactivity of TPO and MPO. Unfortunately studies lack details about the specifics of hyperthyroid episodes so the frequency of thyroiditis over other causes is not clear. There is also a lack of pathological data looking at the thyroid in patients with vasculitis. Recurrent thyroiditis is rare, with cases associated with amiodarone, suppurative thyroiditis and postpartum thyroiditis. To our knowledge this is the first case reported of recurrent thyroiditis associated with vasculitis.

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Choice of diagnosis of solid form of papillary carcinoma in pathological investigation rather than fine needle aspiration

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Thyroid cancer in children at the age of 0–14 year is a rare case and according to 2018 y. sta-tistics, it comprise 4% of total endocrine system cancer. This article describes clinical case of 14 years old boy with the solid form of thyroid carcinoma and the diagnosis was based on the surgical tissue examination. According to planned ultrasound investigation 2 cm nodule was revealed in the left lobe of thyroid gland without involvement in lymph nodules. Blood test of TSH,FT4 hormones was in normal range. Fine needle aspiration (FNA) of the nodules shows thyroid follicular neoplasia. Microscopic investigation revealed a well-surrounded nodule with vascular invasion in capsule. Tumor was composed of round solid nests resembling filled up follicules,surrounded by fibrous/hyaline stroma. Focally nuclear features of papillary carcinoma was presented. Normal follicular structures was revealed arroud the capsule, but in the center of the nodule there was atypical cells with brisk miotoc activity. In the center of the tumor a solid but focally papillary structures was marked. It was performed an additional immunohistochemically (IHC) investigation using 'dako' antibodies : CEA,Calcitonin,Chromogranin A was negative. TTF1, Thyroglobulin and AE1/AE3-positive. It should be signed that poor expression of of the markers is revealed in the mitotic active areas, HBME1 –negative, CD56(-)negative. According to IHC analysis the medullary carcinoma has been excluded, although due to high mitotic activity of tumor cells differntial diagnosis was still followed between poorly differentiated carcinoma vs solid form of papillary carcinoma. It should be noted thyroid papillary carcinoma diagnosed according to nuclear signs of folliculocytes, which is better shown in FNA investigation. The IHC marker with high specifi-city and sensitivity doesn't exist. The morphological criteria performed during investigation, because the cancer was well-surrounded and necrotic areas was not revealed. As the tumor was well-surrounded, there was no necrosis nuclear features of papillary carcinoma detected and given the patient's age, we suggested a solid form of papillary carcinoma. A solid variant of papillary carcinoma may misdiagnosed by FNA investigation which shown more normal cells than tumor cells in smear. That is the first choice of pathological investi gation rather than FNA.

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Hurtle cell carcinoma: A case report

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Background
Hürthle cell carcinoma or oncocytic carcinoma of the thyroid gland is an unusual and relatively rare type of differentiated thyroid cancer. It accounts for only about 3–10% of all differentiated thyroid cancers. Its diagnosis as well as its management remains a subject of controversies.
Aim
The purpose of this paper is to describe clinical presentation as well as the difficulties we can affront within the diagnosis and the treatment of this entity.
Method
We report a case of hurtle cell carcinoma of thyroid gland operated and followed in ENT department of Farhat Hached hospital.
Observation
A 54 year old male with no medical history who undergone thyroidectomy in 2012 for enormous goiter which size have been increasing for 3 years. The anatomopathological examination objectivated oncocytic adenoma on multinodular goiter. the patient was lost to follow up. He presented 5 years later with swelling of the right base of the neck, associated to multiple firm swollen cervical lymph nodes, dyspnea and hemoptysis. A cervico thoracic ct scan showed glottic and supra glottic laryngeal tumor with locoregional extension to thyroid and lungs. An histologic re evaluation redressed the diagnosis to concocytic variant of follicular thyroid carcinoma. The patient has undergone a tumorectomy with an histological examination confirming the diagnosis. A radioiodine therapy and hormone suppressive treatment were completed. Unfortunately the patient was lost to follow up again.
Conclusion
Oncocytic carcinoma is rare with metastatic potential. There are no standard guidelines for its optimal management as few institutions have extensive experience with Hürthle cell neoplasms.

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EP532

The functional state of the parathyroid glands among patients with autoimmune thyroiditis with the presence of calcifications in the thyroid glands

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Thirty five patients (33 women, 2 men) age 26–67 who had calcifications in the thyroid gland in a result of ultrasound examination, the levels of parathyroid hormone, vitamin D and microliters (Ca^{++}, Mg^{++} and Phosphorus) have been determined as well. The level of 25(OH) in the studied groups were significantly reduced and was within the following range; 14 ± 7 ng/ml. Twenty five patients had hyperparathyroidism, which indicated an increased functional state of the parathyroid gland, and 14 patients had the upper limits of the requirement norm ($55 += 5$). Changes in electrolyte metabolism were not determined among examined patients. The possible increased activity of the Parathyroid glands on the background of a low content of 25(OH) is the cause of calcifications in the thyroid gland.

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Hot Topics (Including Covid-19)

EP533

The renin–angiotensin system blockers and the risk of COVID-19

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Introduction
The year 2020 has witnessed a new global pandemic caused by an encased single-stranded RNA virus identified as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The exceptionally infectious capability of the virus, along with case fatality rate ranging from 0.99% to above 3%, have raised major global concerns.
COVID19 and Risk factors
Evidence from several observational studies suggests risk factors for poor COVID-19 patients' outcome. Among these, both Diabetes and hypertension are associated with increased risk. hypertension was the most frequent comorbidity with an estimated prevalence of 15% – 30%.
The renin-angiotensin-aldosterone system (RAAS)
The renin-angiotensin-aldosterone system plays an important role in controlling blood pressure. Angiotensin-converting enzyme (ACE) inhibitors or blockers (ARBs) are highly recommended for the management of patients with cardiovascular diseases. They are also widely used to slow the progress of renal insufficiency in Diabetic patients. These medications together with NSAIDs and Thiazolidinediones can cause upregulation of ACE2

(Angiotensin-converting enzyme 2). Evidence showed increased cardiac ACE2 activity with ACEi/ARBs and increased urinary ACE2 with Olmesartan. ACE2 has been recognized as SARS-CoV-2 binding site to cells. It is not clear if this upregulation of ACE2 is beneficial or harmful. It has been argued that this upregulation could lead to increased patient susceptibility to viral dissemination. Conversely, there is a suggestion that ARB treatment helped reversing the lung injury due to reduction in ACE2 caused by SARS-CoV (the cause of the 2003 pandemic) in mice. A preliminary trial of ACE2 administration to individuals with acute respiratory distress syndrome demonstrated no improvement in lung function. This is a review of the most recent relevant literature on the matter examining several recent observational studies that examined the relationship between ACEI/ARB and COVID19. The reviewed 8 observational studies (with risks of confounding factors) reached the conclusion that there is no sufficient data to advocate stopping ACE/ARB treatment in patients with COVID-19. There were some contradictory findings regarding possible different effects of the two drug classes.
Conclusion
The strong beneficial effects of ACEI/ARB for some patients currently outweigh the theoretical risks. This review supports the British cardiovascular society recent statement that 'Patients should continue treatment with ACEi and ARBs unless advised to stop by their medical team'. This also echoes the American Heart association view on the subject.

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EP534

Prevalence of adrenal tumors in various age groups

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The objective of the research was to study the prevalence of adrenal tumors in various age groups.
Materials and methods
Clinical observation of 282 patients with various adrenal tumors. Among the examined patients there were more women 169(59.9%), with 113 (40.1%) men. The age of patients at the moment of the first application to a doctor varied from 4 months to 74 years old, with average 39.8±15.7 years old. Average age of men was 37.4±16.7 years old, and average age for women was 41.4±14.9 years old. According to WHO age classification presented in 2017 the age under 45 is considered to be young. In relation to that, we distributed the patients to two groups, where we compared clinical case parameters. The first group included 178(63.2%) patients under 45, while the second group involved 104(36.8%) patients ≥45 years old. All patients with adrenal tumors had common clinical, biochemical, hormonal, and instrumental tests.
Results
Adrenal tumors were presented by the following nosological forms: 45(16%) cortisol-secreting tumors, 51(18.1%) pheochromocytoma,16(5.6%) aldosterone-secreting adenoma, 9(3.2%) androgen-secreting tumors, 5(1.8%) adrenal cortical cancer, 11(3.9%) adrenal metastases, and 145(51.4%) incidentaloma. Basic clinical manifestation at the moment of application was arterial hypertension (AH), which was observed in 218 (77.3%) patients and had various expression degrees. Cases of adrenal tumors with increased arterial pressure (AP) did not depend on the age. The average age at the moment of AP rise in the group of patients under 45 was 28.2±8.5 years old, and in the group of ≥45 years old it was 50.0±9.4 years old. Debut of the disease in the group of patients under 45 differed by its sudden start (9.6%), with development of early complications of AH (3.3%). In the group of patients under 45 prevalent duration of AH was less than 5 years, while in the group of patients ≥45 the duration of AH was 5 years and more.
Conclusion
Prevailing majority of patients (55.3%) with adrenal tumors were young at their 18–44 years, in other words in their active workable period, which in its turn, conditions early invalidation and pre-term lethality of the patients in any workability age. In the group of patients under 45 there were more often hormonal active tumors, such as pheochromocytoma (19.1%), cortisol-secreting tumors (23.6%), aldosterone-secreting adenomas (6.2%), androgen-secreting tumors (5.1%), while in the patients of ≥45 years' old there were more incidentalomas (66.4%), metastases (7.7%), and adrenal cortical cancer (2.9%).

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EP535

Pathohistological diagnosis of adrenal tumors: experience of a single center

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Research Objectives
To investigate adrenal tumors of patients operated on at the Osijek Clinical Hospital from 2016 to 2019 to examine the location and histopathological findings of the tumors, and to determine whether there is a difference in the age and gender of the subjects.
Study design
Cross-sectional study with historical data.
Patients and Methods
The subjects were patients of both sexes diagnosed with adrenal tumors who underwent surgery at KBC Osijek in the period 2016–2019. The archive was used in the Clinical Hospital Center Osijek. The results were processed by the statistical program STATISTICA 12.5.192.7.
Results
Adrenal tumors were more often unilateral than bilateral (18 cases, 78%). No differences were found in the localization of tumors of the right and left adrenal glands (9 cases were on the right side, 50%; 9 cases were on the left side, 50%). Benign tumors were more common than malignant and were the most common adenoma (22 cases, 96%). Operated women were on average 10 years older (61.6 years). There were no significant differences with respect to patient age. Benign tumors were more common in women, but the difference was not statistically significant. In the histopathological findings, women were more likely to have adenoma and hyperplasia, while men had more frequently benign tumors and metastatic tumors, but the difference was not statistically significant.
Conclusion
In patients operated on for adrenal tumors, there were more unilateral tumors compared to bilateral ones, but there was no difference in tumor localization (left and right). More common were benign tumors, the most common of which were adenomas. There were no significant differences with respect to age and gender.
Keywords: histology, adrenal glands, adrenal gland neoplasms, adrenocortical adenoma, myelolipoma

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EP536

Primary aldosteronism: follow up of 17 cases

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Introduction
Primary and nonsuppressible hypersecretion of aldosterone is an increasingly recognized, but still underdiagnosed, cause of hypertension. Our objective is to determine the evolution features of primary aldosteronism (PA) patients.
Patients and Methods
Retrospective study of 17 patients with PA confirmed biochemically and histologically when operated.
Results
The mean age was 41.9±9.3 years at PA diagnosis, and 6 of them (35.3%) were male. Twelve patients had adenoma producer of aldosterone (APA), 3 had bilateral adrenal hyperplasia idiopathic (HIA), 1 had familial PA and the last one had primary unilateral adrenal hyperplasia (PUAH). Patients were followed for a period between 6 months and 21 years, with an average of 4.3 years. Eleven out of twelve APA, 1 HIA and 1 PUAH had unilateral adrenalectomy using laparoscopic technique. Of postoperative complications, we noted hypertensive spikes in 5 patients and severe hypokalemia in 2 cases. Eight patients had a remission without antihypertensive drug except

one case with biological 'normo-aldosteronism' and essential hypertension. Familial aldosteronism was treated with dexamethasone. Hypertension was controlled with 2.9±1.2 antihypertensive drugs. An average reduction of 0.9 (range: –1 and 3) in the number of these drugs was obtained in post-therapy; both medical and surgical. All patients had normokalemia. Morbidity was independent of the etiology and the treatment.
Conclusion
The overall treatment goal in patients with PA is to prevent the adverse outcomes. Individualization of treatment according to the anatomo-clinic type determined an improvement of the patients' prognosis without however a significant effect on the morbidity.

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EP537

Peculiarities of clinical progression of aldosterone producing adrenal adenoma

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Introduction
Aldosterone-producing adenoma (APA) in adrenals is relatively rare but diagnostically the most complex hormonal active formation in adrenals. Difficulty of APA diagnostics is that clinically these states are hardly distinguishable from essential hypertonic disease. Besides, it is difficult to differentiate them from several symptomatic arterial hypertensions (AH), such as nephrogenic AH, some types of vascular AH or continuous and mixed pheochromocytoma.
The objective of the research was to study clinical aging characteristics of APA.
Materials and methods. Among the studied patients with various formations in adrenals (n=282), who received out-patient and in-patient treatment in the Republican Specialized Scientific Practical Medical Center of Endocrinology of the Uzbekistan Public Healthcare Ministry within the period from 2000 to 2018, there were 16 patients with APA (5.6%). Among them there were 11(68.8%) women and 5(31.2%) men. The age of patients varied from 20 to 65 years old, with the average age 42.4±12.4 years old. All patients had common clinical, biochemical, and instrumental tests.
Results
Majority of the patients (68.8%) with APA were young workable people, while 18.8% and 12.4% were people of middle and old age, respectively. in relation to gender distribution, APA was 3 times more often observed in female patients. Leading clinical manifestation in all patients with APA in 100% of the cases was AH, which was constant in 75% of the patients, mixed in 12.5%, and in 12.5% of the cases it had constant malignant character. It should be noted, that most often registered among the patients with APA was AH stage I (50%) and AH stage II (37.5%), while only 12.5% had AH stage III. AP values varied from 130/90 to 240/140 mmHg. Maximal level of SAP varied from 160 to 240 mmHg (average value 186.3±28.3 mmHg), DAP from 100 to 140 mmHg (average 111.9±14.7 mmHg). In our observations classical clinical triad including combination of three basic syndromes (AH, neuromuscular, and renal) was noted only in 62.5% of the patients with APA.
Conclusion
Thus, summarizing the obtained data, it can be concluded that, APA was more often met in young workable age with higher prevalence rate among women. Leading clinical manifestation in all patients with APA was AH. It should be noted that, combination of AH, especially in young people, and familiar history of AH and its complications in the closest relatives should serve to be the basis for exclusion of APA diagnosis.

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EP538

Manifestation characteristics of adrenal tumors according to application records in the republic of uzbekistan

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The objective of the research was to study clinical manifestations and characteristics of manifestations of adrenal tumors.

Material and methods
We followed 282 patients with adrenal tumors, who received in and out-patient care in the Republican Specialized Scientific Practical Medical Center of Endocrinology of the Uzbekistan Public Healthcare Ministry within the period from 2000 till 2018. Among them there were 169(59.9%) women and 113 (40.1%) men. The age of the patients at the moment of the first application to doctor varied from 4 months to 74 years old, with average 39.8±15.7. Male average age was 37.4±16.7 years old, while female average age was 41.4±14.9. Adrenal tumors were presented by the following nosological forms: 51(18.1%) pheochromocytoma, 45(16%) cortisol-secreting tumors,16(5.6%) aldosterone-secreting adenoma, 9(3.2%) androgen-secreting tumors, 5(1.8%) adrenal cortical cancer, 11(3.9%) adrenal metastases, and 145(51.4%) incidentaloma.
Results
Adrenal tumors were characterized by heterogeneous non-specific manifestations, such as lumbar pain 12.8%, gaining weight 7.8%, stomachache 5.7%, menstrual cycle disorders 5.7%, losing weight 2.8%, stroke 1.8%, polyuria 1.4%, headache 1.1%, pre-term maturation 1.1%, excessive hair growth 0.7%, cardialgia 0.7%, hypertonic crisis 0.7%, compression fractures 0.7%, neuromuscular disorders 0.4%, with prevalence of arterial hypertension (AH), which was observed in 52.5% of the cases. In 4.1% of the cases there were no symptoms. Taking into account heterogeneity of clinical symptoms, including AH, associated with tumors, most patients first applied to different specialist. Primarily, these patients were treated by other specialists, among them 17.7% of the patients applied first to cardiologist, 14.2% to physician, 8.9% to neuropathologist, 5.7% urologist, 3.5% to gynecologist, 1.8% to oncologist, 1.8% to pediatrician, 0.7% to traumatologist, 0.4% to rheumatologist, and only 18.8% of the patients initially applied to endocrinologist, while in 26.2% of the cases the diagnosis was established by functional diagnostics specialists. In the careful study of the history of the disease we revealed the following: 64.2% of the patients did not link the start of the disease with any reason, 22.7% associated it with stress, 4.6% with pregnancy, 2.8% related it to various surgical interventions, 2.1% with over-cooling, 1.1% with the start of climax period, 0.7% with delivery, infectious diseases, and application of hormonal agents, and, finally, 0.4% with abortions.
Conclusion
Heterogeneity of clinical symptoms, including AH, associated with tumors, inhibit in-time diagnostics due to initial application of patient to other specialists

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EP539

Seizure and coma secondary to Conn's syndrome: A case report

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Background
Conn's syndrome is a curable condition if identified properly. It is characterized by autonomous secretion of aldosterone from the adrenal gland cortex. Its morbidity is related to the increased risk of cardiovascular diseases.
Case presentation
We report the case of a 48 years old male presenting with generalized tonic-clonic seizure and coma secondary to hypertensive encephalopathy. The biochemical evaluation revealed a very high aldosterone level and an undetectable renin level, both are compatible with primary aldosteronism. The presentation of the following: spontaneous hypokalemia, an undetectable renin level, and a high aldosterone level confirms the diagnosis of primary aldosteronism. Abdominal computed tomography revealed a left adrenal adenoma. Adrenal venous sampling confirmed lateralization of aldosterone excretion from the left adrenal gland. The patient underwent left laparoscopic adrenalectomy that confirmed a left functional adrenal adenoma. After 12 months of follow up, the patient's hypertension was controlled on only one antihypertensive drug down from four drugs preoperatively.
Conclusion
Conn's syndrome, in this case, was complicated by coma secondary to seizure. Adrenalectomy has normalized the hypokalemia and improved resistant hypertension. Potassium supplementation and several antihypertensives were discontinued as the patient became normokalemic and normotensive on one antihypertensive agent.

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EP540

Hyperaldosteronism in a female with chronic hypokalemia

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Introduction
Hyperaldosteronism is not so common in middle-aged groups. But it should be concerned in the case of unclear hypertension, fatigue, or dyspepsia.
A 61-year-old female was hospitalized in the private clinic 'Oberig' in December 2019. She had non-specific complaints such as weakness, dyspepsia, constipation, vomiting, losing an appetite, decrease in body weight. She has been treated for a long time out-patiently and had some episodes of hospitalization, including the surgical unit. She had severe electrolyte disorders, such as hyponatremia (106 mmol/l), hypokalemia (1.8 mmol/l), hypochloremia (62.8 mmol/l), hypophosphatemia (0.54). Magnesium was normal (97 mmol/l). AKSH and cortisol were in the normal range. She has arterial hypertension since being 25–30 years old. She was reported to have multinodular goiter for four years. She received levothyroxine 50 mg daily, but we detected that TSH was slightly less than average (0.36). There was a decision to decrease the dosage to 25 mg with further TSH control in 1 month. After normalization of the potassium level in the blood, we checked aldosterone and renin. Aldosterone was normal, renin was less than average, and their correlation was increased up to 37 (normal range is lower than 18.7). Adrenal hyperplasia was not detected on CT. We prescribed eplerenone 50 mg. Soon in 1 month, all symptoms regressed, and the patient felt much better.
Conclusion
Electrolyte screening is essential for diagnostic unclear dyspepsia and hypertension.

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EP541

How to treat primary hyperparathyroidism in pregnancy? A case series

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Primary hyperparathyroidism (PHPT) is rare in pregnancy, with an incidence of 1%. It is associated with maternal, fetal, and neonatal complications. Treatment options include both medical and surgical approaches. Parathyroidectomy is the definitive and preferred treatment, especially when serum calcium level is higher than 10.8 mg/dl and with a prior history of pregnancy loss. Herein, we present two cases of gestational primary hyperparathyroidism with different treatments.
Case one
A 40-year-old lady G5P3023 at 30 weeks of gestation who presented with epigastric. Initial workup revealed serum lipase of 1256 u/l and serum calcium of > 15 mg/dl with normal serum albumin. Further workup for hypercalcemia showed an elevated ionized calcium level of 2.04 mmol/l, PTH of 350 pg/ml, Vitamin D 1–25 dihydroxy level of 43.1 pg/ml, vitamin D 25 hydroxy level of 15.9 ng/ml. She received intravenous fluids for acute pancreatitis. Ultrasound of the neck revealed a 1.9 × 1.6.1.7 cm nodule suspicious for parathyroid adenoma. The patient received aggressive IV fluid resuscitation, two intramuscular injections of 300 units of calcitonin, and 60 mg of cinacalcet twice daily. Despite medical management, her serum calcium level remained elevated for a week, requiring and a right inferior parathyroidectomy. After surgery, her serum calcium level normalized.
Case two
A 30-year-old lady G1P1001 at 40 weeks of gestation who presented with concerns of decreased fetal movements. She underwent emergent cesarean due to non-reassuring fetal heart tones. The infant was born with hypoglycemia. Initial workup was significant for serum calcium of 14.1 mg/dl with normal serum albumin. Given the hypercalcemia, the patient received aggressive intravenous fluid resuscitation, 200 units of subcutaneous calcitonin twice daily, 30 mg of cinacalcet twice daily. Further workup for hypercalcemia showed ionized serum calcium level of 1.61 mmol/l, PTH of 302.6 pg/ml, vitamin D 25 hydroxy level of 20.4 ng/ml. Her hypercalcemia manifested as several episodes of coarse upper and lower extremity tremors. An ultrasound of the neck illustrated a 2.5 × 2.5 cm parathyroid nodule consistent with a parathyroid adenoma. Despite medical management, serum calcium levels remained high after a week. She underwent left inferior parathyroidectomy, and her calcium levels normalized after the surgery.
Compared to conservative management, surgical treatment with parathyroidectomy is associated with better maternal and fetal outcomes, as it has shown a decreased incidence of pre-eclampsia and preterm delivery. Hence, gestational hyperparathyroidism is a clear indication for an early parathyroidectomy in both symptomatic and asymptomatic patients.

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EP542

COVID-19 infection in a patient with life-treatening hypercalcaemia and sickle cell disease

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A 21-year-old woman with homozygous sickle cell disease, presented to A&E with vomiting and diarrhoea, and was noted to be hypercalcaemic (corrected calcium 3.00 mmol/l [ref. 2.2–2.6]; phosphate 0.48 mmol/l [ref. 0.8–1.5]). She reported polyuria and polydipsia, but no other symptoms of hypercalcaemia. There was no history of renal stones, renal impairment, or fragility fracture. A maternal aunt required parathyroidectomy in middle age. Bloods revealed PTH 138.4 pmol/l (ref. 1.6–6.9), magnesium 0.6 mmol/l (ref. 0.7–11.0), Vit D <13 nmol/l and normal pituitary function. 24-hour urinary calcium was elevated at 9 mmol/day (2.5–7.5). A calcium creatinine clearance ratio of 0.0131 ruled out familial hypocalciuric hypercalcaemia. The hypercalcaemia responded to intravenous fluids and she was discharged on cinacalcet and cholecalciferol. Three days later she represented with a further sickle cell crisis. Bloods showed persistent hypercalcaemia 2.67 mmol/l, with an acute haemoglobin drop from 82 to 58 g/l (ref. 120–150). The patient was transfused and restarted IV fluids. Following transfusion, hypercalcaemia worsened, peaking at a level of 3.77 mmol/l, refractory to IV fluids, withdrawal of cholecalciferol, and an increase in cinacalcet dose, but responded to IV bisphosphonates. Admission was compounded by a delayed haemolytic transfusion reaction. Localisation studies were performed: there was no abnormal parathyroid tissue on neck ultrasound, but CT and Tc99m-sestamibi scanning both suggested a 4.4 cm upper mediastinal parathyroid mass. Emergency parathyroidectomy was planned, but postponed when pre-operative COVID-19 screening returned a positive nasal swab. Surgery was further delayed by an admission with hyperhaemolysis, but was performed 4 weeks later. The post-operative course was complicated by severe, symptomatic hypocalcaemia, and sickle chest crisis. Imaging was consistent with COVID-19 pneumonia, despite a then negative nasal swab. Management of hypocalcemia with IV calcium infusions worsened the degree of haemodilution and increased the potential for precipitating a crisis. Conversely, blood transfusion increased the risk of hyperhaemolysis. Hungry bone syndrome is likely to underly the intractable hypocalcaemia, which was exacerbated by vitamin D deficiency. Additionally, COVID-19 pneumonia increased the risk of precipitating a crisis. Histology was in keeping with an atypical parathyroid adenoma, with scattered mitoses and a Ki-67 of 20%.
Discussion
– Role of vitamin D replacement in hyperparathyroidism.
– Concerns about malignancy in a young patient with very elevated calcium and PTH.
– Complications of GA, surgery, and post-operative calcium replacement in sickle cell patients.
– Surgical planning in times of COVID-19 and dealing with COVID-19 sequelae.
– Role of genetic studies.

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EP543

Are women with osteoporosis treated with denosumab at risk of severe COVID-19?

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Coronavirus disease 2019 (COVID-19), is a primarily respiratory infection which can lead to severe syndrome needing hospitalization and assisted ventilation with high lethality. In a recent meta-analysis of 33 RCTs increased risk of severe infections on treatment with Denosumab, widely used for treatment of osteoporosis, was found specifically for ear, nose, and throat. In fact, by inhibiting the receptor activator of nuclear factor κ-B ligand, denosumab acts as an immune system modulator. However, despite these findings calling for caution, several recently published opinions recommended maintaining treatment with denosumab during the COVID-19 outbreak, We report on the incidence of symptomatic respiratory infections in denosumab vs other available drug treated osteoporotic population attending our bone clinic in Milano one of the centers of COVID-19 pandemic in Italy. We conducted a telephone interview on a sample of 85 patients (aged ≥18 years) regularly followed in our bone center for post-menopausal osteoporosis ($n=75$) or under aromatase inhibitors (AI) for breast cancer ($n=10$). We excluded patients with comorbidities and concomitant therapies potentially influencing COVID-19 morbidity such as chronic kidney disease and glucocorticoid treatment. All patients were asked the following questions concerning the 3 month period from February 21 to May 24.2020: 1. clinical symptoms of upper airway infection or diagnosis of pneumonia, 2. COVID-19 positive testing, hospitalization and related clinical course; 3. Falls. A total of 50 patients responded to the survey. Fifteen were treated with oral bisphosphonates (BP; mean age 68.8±11.4), 29 with denosumab (D; mean age 79.2±8.6) and 6 with teriparatide (T; mean age 75.0±10.4). Median duration of treatment was 7, 26 and 10 months respectively. In the BP and D group: one patient reported self-limited fever and cough, none of the patients was hospitalized and two and one patient respectively reported one episode of fall without clinical consequences; in T group no patients reported symptoms of infection, hospitalization or falls. Our preliminary data suggest that denosumab may not represent specific risk factor for COVID-19. Our data give some initial real life evidence support to opinions which recommended to continue denosumab during COVID-19 pandemic. Interestingly, it can be hypothesized that female sex may have exerted a relevant protective effect. Finally, it can not be excluded a selection bias in the choice of our patients for denosumab treatment excluding a priori those with recurrent or at increased risk for respiratory infections.

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EP544

Frequency of musculoskeletal complications in patients with acromegaly in the Ferghana Valley

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The aim of the study was to study the incidence of osteo-articular complications in patients with acromegaly in the Ferghana Valley.
Materials and methods
129 patients with acromegaly in the Ferghana Valley who were included in the national register of acromegaly were examined. Of these, men – 46 (35.7%), women – 83 (64.3%). The average age of the patients was (48±8.7 years). By age, patients were divided into three groups: 1 group – up to 30 years, 2 gr. –30–44 years, 3 gr. – 45 years and older. The diagnosis of acromegaly was established on the basis of the clinical manifestations of the disease and was confirmed by high serum levels of GH, IGF-1 levels
Results
According to the national register of patients with acromegaly, 2019(Republic of Uzbekistan), the incidence of osteoarticular neuromuscular complications was 82.9%, osteoarticular neuromuscular complications were most common among patients with acromegaly – arthropathy (57.4%), followed by carpal tunnel syndrome (49, 6%) and osteoporosis (48.9%). At the time of diagnosis, in most cases (more than 2/3 of cases) macroadenomas are detected, which may be associated with a delayed diagnosis and imposes difficulties in surgical treatment of these tumors. As the results showed, the examined patients had a high frequency of macroadenomas, with their prevalence in the Andijan (47.5%, $P<0.05$) region. In general, macroadenomas and giant pituitary adenomas are more often identified in patients of Ferghana Valley.
Conclusion
In the Ferghana Valley, acromegaly prevails among women, while acromegaly is common over the age of 45 ($P<0.05$) years in all regions of the Ferghana Valley. The highest frequency of MSC was identified in the Ferghana region, followed by the Namangan region and the frequency of MSC in Andijan region is relatively lower. Macroadenomas were more often present in patients with acromegaly of the Ferghana Valley, with their prevalence in Andijan region.

Keywords: acromegaly, musculoskeletal complications, arthropathy, osteoporosis
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EP545

An unexpected cause of severe hypocalcemia

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Background
Common Variable Immunodeficiency syndrome (CVID), the most common symptomatic immunodeficiency in aduIts, is characterized by diminished levels of IgG, IgA and/or IgM, and recurrent bacterial infections. The gastrointestinal (GI) manifestations of CVID are rare and variable. We herein report the case of a patient with a severe hypocalcemia secondary to digestive tract involvement of the CVID syndrome.
Case report
A 32 year-old female patient with a history of CVID and recurrent lung infections was admitted to our department for exploration of deep hypocalcemia. She complained of weight loss, asthenia and paresthesia of the lower limbs.She also reported abdominal pain and diarrhea. The physical examination revealed a weight a body mass index of 17.6 kg/m^2 and a a homogeneous hepatosplenomegaly. Trousseau sign was elicited. Biochemical tests noted hypocalcemia of 57 mg/l, hypophosphoremia of 10 mg/l, hypokalemia of 2.7 mmol/l, hypomagnesemia of 10 mg/l and hypoalbuminemia of 25.8 g/l. Hypochromic microcytic anemia of 7.9 g/dl was also found. The hormonal assessment revealed hyperparathyroidism secondary to vitamin D deficiency. Thyroid assessment and coeliac disease serology were normal. Electrocardiogram showed sinus tachycardia, an elongated QT space and diffuse negative T waves. Upper endoscopy and duodenal biopsy were normal. Computed tomography enterography didn´t show any thickening of the bowel wall. Colonoscopy showed a normal appearance of colonic mucosa but colonic histology revealed a chronic colitis with moderate activity related to its CVID syndrome.
Conclusion
GI manifestations in CVID are mainly dominated by chronic diarrhea. This diarrhea can be due to chronic infections with Giardia lamblia but also resulting from specific lesions of the intestinal mucosa such as villous atrophy mimicking celiac disease.

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Maternal and foetal outcomes associated with medical and surgical treatment of primary hyperparathyroidism in Pregnancy

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Background
The management of Primary hyperparathyroidism (PHPT) during pregnancy is challenging due to lack of robust guidelines. Various studies have suggested an increased risk of various maternal and foetal complications, however there is no clear consensus in the literature about medical treatment vs surgery during pregnancy. The aim of this study was to review the maternal and foetal outcomes of pregnant women treated for PHPT at a single tertiary care centre and compare our findings with similar studies in the literature.
Methods
Data on relevant clinical parameters, demographics, management strategies, maternal and foetal outcomes were collected from pregnant patients with PHPT between 2012 and 2019.
Results
Of 15 pregnancies with PHPT that were reviewed, 6 were managed medically and 9 patients underwent surgery during pregnancy. The median age at

index pregnancy was 28 years (range 19–42). The median highest recorded adjusted calcium in the medical group was 2.90 mmol/l (2.61–3.25) while it was 3.11 mmol/l (2.78–4.95) in the surgical group. There was one miscarriage and stillbirth of a twin pregnancy in the medical group, but none in the surgical group. The median gestational age at delivery (excluding miscarriage) was 39+3 (24+2–41+2) and 39+4 (37+1–39+5) in the medical and surgical groups respectively. There was one emergency C-section in each group. None of the live births in either groups were complicated with neonatal tetany or convulsions. All the surgeries were successful with no reported post-operative complications.
Conclusion
This study and the review current literature suggests that more complications appear to occur in the medically treated pregnant PHPT patients, however the evidence is not conclusive. Most surgeries during pregnancy are performed during the second trimester with good outcomes. Multi-centre prospective studies are required to ascertain the exact risk of various complications for PHPT during pregnancy.

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Familial Isolated Hypoparathyroidism caused by AIRE gene mutation

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Hypoparathyroidism is an uncommon condition characterized by reduced parathyroid hormone production resulting in hypocalcaemia with its clinical manifestations. A minority of cases are familial and exist as either isolated disease or as part of well described, multisystem syndromes. Mutation in the Autoimmune regulator gene (AIRE) results in Autoimmune Polyglandular Syndrome type 1 featuring hypoparathyroidism as a part of the syndrome. This case reported herein describes a mutation in AIRE leading to Isolated hypocalcaemia with an otherwise normally functioning endocrine glands.

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Teriparatide treatment in a patient with resistance hypoparathyroidism

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Background
Hypoparathyroidism is an uncommon disorder of calcium metabolism characterized by hypocalcemia, hyperphosphatemia, and reduced level of parathyroid hormone (PTH). The most common cause of hypoparathyroidism is accidental damage to the parathyroid glands during thyroid surgery. There are no formal guidelines for hypoparathyroidism management. The main goal of treatment is to improve the symptoms of hypocalcemia, to keep the serum calcium within the low normal range, and to avoid hypercalcemia. Herein we report a case of hypoparathyroidism, which was successfully treated with subcutaneous teriparatide.
Case report
A 38-year-old woman presented to our clinic with tetany. The patient had symptoms of perioral numbness, paresthesias of the hands and feet, muscle cramps, and Chvostek's sign was positive. It was learned that one year before admission, the patient underwent a total thyroidectomy due to multinodular goiter, and treatment was given for hypoparathyroidism related to post-surgical hypoparathyroidism. The patient, who received 6 gr calcitriol and 12 gr calcium carbonate treatment, was hospitalized with the diagnosis of resistant hypoparathyroidism. The laboratory values were PTH:1 pg/dl, Ca:6.1 mg/dl, phosphorus: 5.1 mg/dl. Normocalcemia was achieved, and hypocalcemia signs and symptoms regressed with intravenous calcium treatment. 25(OH)D and hydrochlorothiazide treatment were added to the treatment of the patient, and calcium carbonate treatment was started to be given as 2 g at 4-hour intervals. Despite treatment changes, the patient's calcium level was found to be 7.8 mg/dl. Teriparatide treatment was started for the patient who stated that using high dose calcium treatment affects the quality of her life. The patient was started on 2*20 mg teriparatide treatment, and daily serum calcium level control was performed. Calcitriol treatment was discontinued within two weeks, while Ca treatment was reduced to 1 g. Although the patient described mild bone pain lasting up to 1 hour with teriparatide treatment, the patient's symptoms and signs of hypocalcemia did not recur. The patient, whose treatment was adjusted as 2*20 mg teriparatide and 2 g calcium carbonate, did not need intravenous calcium treatment for six months. Before starting teriparatide treatment, the patient's 24-hour urinary calcium level was 231 mg/day, and after three months, it decreased to 91 mg/day with teriparatide therapy. Although the patient states that mild bone pain persists, she describes that the quality of life has improved greatly.
Conclusion
Teriparatide is an effective alternative treatment for patients with hypoparathyroidism, which may avoid the potential side effects of conventional therapy.

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Precocious pseudopuberty with central progression due to McCune-Albright Syndrome: case report

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McCune-Albright Syndrome (MAS) is a rare congenital sporadic disorder due to an embryonic post-zygotic somatic mutation in the GNAS1 gene, defined by the triad of peripheral precocious puberty (PPP), unilateral café-au-lait spots and fibrous dysplasia (FD) of bone. PPP or precocious pseudopuberty is the most common endocrinopathy seen in MAS. Other hyperfunctioning endocrinopathies include hyperthyroidism, acromegaly, FGF23-mediated hypophosphatemia and neonatal hypercortisolism. A 2.6-year old girl with history of a recent 15 mm left ovarian cyst was admitted for repeated vaginal bleeding and slightly elevated growth rate. Physical examination: bilateral thelarche Tanner stage 3, menarche, advanced stature+0.94 s.d. towards the mean, lumbosacral, café-au-lait spots without axillary-pubic hair or bone deformities. MAS was assessed. Hormonal evaluation: basaline estradiol (E2) values fluctuated between 10.7–71.5 pg/ml, with reduced serum gonadotrophin (LH≤0.13 mUI/ml, FSH≤0.21 mUI/ml), normal TSH, FT4, PRL, IGF1, basal cortisol, testosterone, DHEAS, 25-OH vitamin D, slightly elevated 17-OH progesterone (2.6 ng/ml), low PTH (14 pg/ml) associated with normal serum phosphorus and calcium, high alkaline phosphatase (599U/l) and osteocalcin (66.7 ng/ml). The first Diphereline stimulation test (DST) 0.1 mg SC showed LH=0.68 mUIm/l at 4 h. The 6 month DST was positive with an increasing tendency of gonadotrophin suggesting central puberty (LH and FSH at 4 h were 4.5 mU/ml respectively 7.19 mU/ml) and E2=68.8 pg/ml at 24 h. Abdominal ultrasound: enlarged uterus of 7.5 cc, 41 mm, thickened endometrium, no ovarian cysts, normal adrenal glands. Breast ultrasound: 13.6/15.8 mm right and 16.7/15.5 mm left breast buds. Bone age: 4 years old. Cranial CT scan and pelvic, bilateral femur and knee X-rays: polyostotic fibrous dysplasia of the neuro- and viscerocranium, bilateral iliac and femoral neck and left proximal tibial osteosclerosis areas. Pituitary MRI and thyroid ultrasound were normal. The prescribed treatment consisted of Letrozole 1.5 mg/m^2/day associated with Diphereline 1.87 mg/28 days and 1-alphacalcidol 0.25 µg/day. One month later, follow-up revealed: disappearance of vaginal bleedings and normal E2. PPP in girls results from autonomous ovarian tissue activation with recurrent estrogen-secreting ovarian cysts. Due to prolonged exposure to high E2 levels with maturation of the hypothalamic-pituitary axis, PPP may progress to central precocious puberty (CPP). Treatment includes aromatase inhibitors alone or in combination with gonadotropin-releasing hormone agonists. FD is associated with increased osteoclastic activity and elevation of biochemical markers of bone turnover. Bisphosphonates have been alleged to improve FD symptoms in MAS. As the age of onset and the severity of the MAS clinical manifestations are variable, close long-term follow-up and periodical screening are required. Therefore MAS management is challenging and involves a multidisciplinary team.

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Review of the histopathological findings of operated tumors of the parathyroid glands and patients data: A single Centre experience

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Introduction
Parathyroid gland proliferative disorders include adenoma, hyperplasia and carcinoma. Adenoma and hyperplasia are found more commonly in women, while carcinoma, which is very rare, is found in both sexes equally. The aim of this study was to investigate parathyroid gland tumors surgically removed at University Hospital Centre Osijek between 2016 and 2019. Also to review tumor location, size and histopathology and compare sex difference.
Patients and methods
Patients of both sexes undergoing parathyroidectomy for parathyroid gland tumor in University Hospital Centre Osijek between 2016 and 2019 were included in the study. Parathyroid gland tumor samples were histologically analyzed, their size and histopathology were noted. Existing documentation on patients with parathyroid gland tumor was used. Analyses was done on archived histologic material stained with hematoxylin – eosin stain. Statistical analysis was done on MedCalc Statistical Software version 18.9.
Results
Overall 19 samples of parathyroid gland tumor were included in this study. Tumors of the parathyroid glands are most commonly localized on the lower left parathyroid (8 cases, 42%), and most rarely on the upper right (2 cases, 11%). The histopathological diagnosis was most commonly determined by adenoma (11 cases, 58%), followed by hyperplasia, while no cancer was diagnosed. Tumors were operated more frequently on women than on men (17 vs 2 cases). There was no correlation in histopathology of parathyroid tumor and sex (Fisher's Exact Test, $P=1$). And there was also no correlation in tumor location and sex (Fisher's Exact Test, $P=1$).
Conclusion
The most common locations of tumors of the parathyroid glands were the lower glands, the more frequent was the lower left parathyroid and most often it was an adenoma. Women are more frequently operated on than men.
Keywords: parathyroid glands, primary hyperparathyroidism, histopathology, staining and labeling

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Metabolic profile of a diabetic population on statins

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Introduction
Dyslipidemia is a frequent pathology, especially in diabetics, which may require the use of lipid-lowering drugs such as statins. Our goal is to determine the impact of these molecules on the metabolic profile of a diabetic population with dyslipidemia.
Methods
This is a retrospective study including 150 patients followed at the Tunis nutrition institute for diabetes and dyslipidemia.
Results
The average BMI was 31.4±6.1 kg/m². Waist circumference was high especially among women. Over three-quarters (76%) of the patients were hypertensive. Average fasting glucose was 13.12 mmol/l with extremes ranging from 5.3 to 24.9 mmol/l. The average HbA1c level was 9.62±2.16%. The mean duration of statin therapy was 2.2±2.6 years. After being put on statins, the average BMI and waist circumference both increased significantly ($P=0.007$ and $P=0.029$ respectively). Both systolic and diastolic blood pressure increased but not significantly. Fasting blood sugar became significantly higher ($P=0.039$). The average HbA1c decreased but this decrease was not significant. Regarding lipid parameters, total cholesterol decreased by 1.02±1.25 mmol/l ($P<0.001$). Triglyceridemia decreased but not significantly ($P=0.15$). HDL cholesterolemia decreased by 0.035±0.27 mmol/l without this being significant. The uricemia also decreased under statins but not significantly.
Conclusion
Statins have modified the metabolic profile of our population, especially anthropometric and biological parameters, which underlines the importance of clinical and biological monitoring after taking these molecules.

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Vitamin D deficit in type 2 diabetes patients during COVID-19 lockdown with and without supplementation

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Introduction
Low vitamin D status has been associated to COVID-19 risk, and type 2 diabetic patients are a vulnerable group. Even though the Canarian archipelago is one of the sunniest spots in Europe, our prevalence of vitamin D deficit is known to be very high. The mandatory lockdown may have worsened this deficit, increasing the need for vitamin D supplementation.
Objectives
Our main objective was to assess and compare the prevalence of vitamin D deficit in supplemented and unsupplemented type 2 diabetic patients from Northern Gran Canaria during the 12 week lockdown started on March 15th 2020. A secondary aim was to correlate the strike rate of COVID-19 with the calcifediol status of the patients.
Methods
Plasma calcifediol levels were sampled in an unselected type 2 diabetic population, along with age, gender, vitamin D supplementation status and confirmed COVID-19 status.
Results
Data were obtained from 239 consecutive patients, 140 female (58.6%), mean age 57.9±16.7. 97 (40.6%) were taking vitamin D supplements years. Mean plasma calcifediol was 30.1±13.2 ng/ml; but it was lower than recommended (<30 ng/ml), in 57.3% of the patients, deficient (<20 ng/ml) in 22.2% and severely deficient (<12 ng/ml) in 5.0%. In supplemented patients, calcifediol was mostly adequate (mean 41.0±12.4 ng/ml, with 22.7%<30 ng/ml, 4.1%<20 ng/ml, none<12 ng/ml and none>80 ng/ml) but low in unsupplemented patients (mean 22.7+7.3 ng/ml, with 81.0%<30 ng/ml, 34.5%<20 ng/ml and 8.5%<12 ng/ml). Plasma calcifediol was significantly higher in supplemented patients (unpaired t-test, $P<0.0001$) and the proportions of low, deficient and severely deficient patients were significantly lower (Fisher's exact test, $P<0.0001$, $P<0.0001$ and $P=0.0062$, respectively). The strike rate of COVID-19 was fortunately very low in this population (1.26%) with 3 confirmed cases (all of them mild, 2 in unsupplemented and 1 in supplemented patients), and though numerically lower in supplemented patients (1.03% vs. 1.41%) it could not be meaningfully analyzed.
Conclusions
With a mandatory lockdown right after the winter months, the prevalence of low calcifediol levels in our unsupplemented type 2 diabetic population is extremely high. On the other hand, when taking vitamin D supplements their vitamin D status is satisfactory with<5% deficient patients and none severely deficient. We cannot conclude that vitamin D supplements were associated with protection from COVID-19; however, their use was effective to prevent the deprivation associated with lockdown.

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Higher HbA1c increases mortality in COVID 19 swab positive hospital inpatients with diabetes

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Introduction
In the UK, the North West of England is one of the worst affected regions by COVID 19, with over 275 cases/100,000. We retrospectively looked at the diabetes characteristics of consecutive patients at our trust admitted with COVID 19 and had known diabetes, and assessed whether there was a correlation with the outcome, Clinical Frailty Score (CFS) and age.
Methods
88 continuous patients with a prior diagnosis of diabetes and COVID 19 swab positive requiring inpatient stay were included. Primary care records provided information on HbA1c. Inpatient records were interrogated to obtain information on CFS (1–9), diabetes drugs and outcome. A Cox's proportional hazards regressional model was used to evaluate the results.
Results
One patient was excluded. Male:female ratio 54:33. Mean age 75.9 years. Mean CFS 5.06. At time of analysis, 43 patients had died, 39 discharged and 5 still inpatients. 68 patients had a history of hypertension. No obesity data was available. Mean HbA1c was 53.2 mmol/mol. 38 patients took metformin, 22 DPP4-inhibitors, 12 sulphonylureas, 6 GLP-1 analogues, 5 SGLT2-inhibitors, 1 pioglitazone, and 12 insulin. 2 patients were admitted with glycaemic emergency (1 DKA, 1 hypoglycaemia). An increase in HbA1c ($P=0.034$) and a CFS<5 ($P=0.0285$) were associated with an increased risk of mortality. A 1 mmol/mol increase in HbA1c was associated with a 10.8% increase in mortality (CI 1.008–1.2192). No correlation between age and HbA1c, and CFS and HbA1c were found.
Discussion
This study adds to the evidence base regarding the importance of diabetes control and COVID outcome. A number of questions arise however, including the role of non-diabetic hyperglycaemia and outcome, and the balance of very tight control vs hypoglycaemia. Prospective interventional studies are also required to look the impact of various levels of inpatient glucose control and outcomes. There was insufficient data to look at the impact of individual diabetes drug classes. The unexpected finding of a lower CFS score (ie less frail people) having a higher mortality (converse to expectation) may be explained by a number of factors, including a low number of patients with low CFS, subjectivity regarding the CFS by many different clinicians on assessment, and a small sample size. It is also possible that those less frail patients who need hospital admission are generally very unwell, as compared to older multimorbid frailer patients who may be admitted with lower levels of illness.
Many thanks to Luigi Sedda, Alison Unsworth & Abdul Ashish
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Patient reported changes in metabolic health during COVID-19 induced lockdown – a cross sectional digital connect survey in type 2 diabetes

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Introduction
During the COVID-19 induced lockdown it is imperative that people with T2DM be aware, disciplined, and sensitive to achieve glycemic control to mitigate the risks of COVID 19.
Methods
We conducted a cross sectional survey to map the overall short-term impact of nationwide lockdown on the metabolic parameters and change in healthful behaviour patterns among patients from pooled practices of 21 diabetologists across 343 patients, with 30 questions designed to assess the current health status, perceived health status and behaviour before the lockdown and change observed in health status after 21 days of lockdown.
Results
Mean age was 55 years ± 13.0 (95% CI 52 to 55). Participants in aged 18–60 years were more often primary earning members ($n=176$) as compared to age group >60 years ($n=57$) (OR 2.48, 95% CI 1.53 to 4.02; $P<0.0003$) and less likely to have duration of diabetes >10 years ($n=80$) (OR 0.10 95% CI 0.06 to 0.17, $P<0.0001$). Almost half were non-hypertensives ($n=157$) between age group of 18–60 years (OR 5.46 95% CI 3.28 to 9.06, $P<0.0001$). There was not much change in number of participants aged >60 years, that had adequate sleep duration even during lockdown (32 vs 33) (OR 0.32 95% CI 0.17 to 0.62, $P<0.0009$), whereas almost one fourth ($n=88$) who had adequate sleep duration during lockdown were aged 18–60 years. There were less proportion of females ($n=51$) on insulin as compared to males ($n=65$) (OR 0.44 95% CI 0.28 to 0.71, $P<0.0009$). There was dramatic drop in females (105 vs 5) ordering food from eatery as compared to males (205 vs 28) (OR 0.34 95% CI 0.14 to 0.9, $P=0.03$). Fasting glucose reported by SMBG >140 mg/dl, by 32.6% before lockdown, changed to 18%, during lockdown. Participants reporting decrease in weight (16.3%) were more than those reporting increase in weight (14.8%), despite 7.7% less participants reporting daily physical exercise during lockdown. There were 81% and 74% increase in people who were unable to SMBG for fasting and post prandial glucose, respectively.
Conclusions
Our study highlights the dynamic impact of the lockdown which enabled a situational, self-automated patient empowerment driven despite limited resources, to enable control of diabetes. The results need corroboration with a longer follow up to evaluate changes with the evolving COVID 19 environment.
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Maturity-onset diabetes of the young type 5 (MODY 5): A case reporte

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The diagnosis of atypical non-autoimmune forms of diabetes mellitus, such as maturity onset diabetes of the young (MODY) presents several challenges, in view of the extensive clinical and genetic heterogeneity of the disease. In this report we describe a case of atypical non autoimmune diabetes associated with a damaging HNF1β mutation. A 39-years-old woman with normal weight (BMI 20'8 kg/m^2), endometriosis, ex-smoker, fatty liver and uterus bicornis unicollis surgery performed 10 years before was consulted to the emergency department complaining of fever and tachycardia. The blood test evidenced leukocytosis, high inflammation markers (fibrinogen and C-reactive protein) and glucose levels (487 mg/dl), without venous blood gas alterations. Urine test showed positive nitrites, ketone bodies and bacteriuria, and a urinary tract infection was diagnosed. The patient was admitted to Internal Medicine department for antibiotics and to perform a complete study. It revealed high glycosilated hemoglobine (HbA1c) levels (11'8%), and revieweing last 10 years blood tests, impaired fasting glycemia was found. Ecography revealed multiple renal cysts. Asking about symptoms of hyperglycemia, the patient referred polyuria, polydipsia and weightloss over the last 3 months. Six days later, there was no sign of infection neither complication, glucose levels became normal and she felt better. The patient performed a short-term diabetes education program and was discharged with multiple-dose insulin injection therapy. Two weeks later, negative antibodies for GAD and islet cell antibodies (ICA) and low C-peptide leves were obtained, suggesting a low insuline secretory reserve, and she was diagnosed with a type 2 diabetes. The patient referred a paternal history of diabetes (grandfather, grandmother and uncle) but she could not specify the type of diabetes neither the establishment age. Because of that multiple-dose insulin injection therapy was replaced by a basal insuline dose and a combination of metformin and dipeptidyl peptidase-4 inhibitor (iDPP4) was introduced. Three months later the patient reduced 60 percent of the total daily insuline dose, HbA1c levels became normal (5'2%) and fasting capillary blood glucose were under 100 mg/dl. Because all of that we applied for a genetic testing for MODY, that shown a HNF1β de-novo mutation (her mother and sister were negative for the mutation, her father would not perform the test). The optimal care for patients with MODY-5 is multidisciplinary and involves obstetricians, endocrinologists, geneticists and nephrologists. That's why from our point of view all of them should be aware of this condition due to its potential complications.
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GABA from medical nutrition to pancreatic beta-cell regeneration

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GABA from medical nutrition to pancreatic beta-cell regeneration.
Introduction
Type 1 diabetes is considered as one of the most widespread chronic diseases in the world, which happens due to autoimmune damage of beta cells in islets of langerhans in the pancreas. It is the most widespread type of diabetes in young age below 18 years(1.2).The beginning or progress of autoimmune cellular injury of pancreatic beta cells could occur through the presence of many auto-antigens which are detected in the pancreatic beta cells(12).it was found that GABA promoting proliferation of beta cells which may have good impact on type 1diabetes(21).
Design
Randomized, controlled trial, 6 month trial.
Materials and Methods: 100 type 1 diabetes patients were randomized into 2 groups.
Result
The results exhibited a statistically significant decrease of anti-gad antibodies and a statistically significant increase of c peptide levels after 6 months of treatment with GABA.
Conclusion
GABA may be used for decreasing anti-gad antibodies and beta-cell regeneration.

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Use of metformin in patients with type 2 diabetes mellitus

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Background
Metformin is the most known oral glucose-lowering medications. It is considered to be the optimal first-line treatment for patients with type 2 diabetes mellitus.
Goal
The aim of the study was to describe the clinical and biological profile of patients with type 2 diabetes mellitus treated with metformin.
Methods
This was an observational study conducted among 57 patients with type 2 diabetes mellitus. It was performed between January and March 2020 in the outpatient department of the national institute of nutrition. Patients with creatinine clearance less than 30 ml/min were not included.
Results
The mean age was 61.3±8.65 years. Sixty-three percent were women, 37% were smokers or ex-smokers and 91% were having high blood pressure. The mean duration of diabetes was 16.2±7.5 years. The average HbA1c was 10.5±1.5%. Thirty-nine patients (68%) were taking metformin. One third of patients treated with insulin were not taking metformin. Patients treated with metformin had significantly shorter duration of diabetes (14.7±7.1 vs 19.3±7.8; p=0.044), higher creatinine clearance (96.1±19.2 ml/mn vs 81.9±21.1 ml/mn; P=0.010)and higher fasting blood sugar (2.49±0.7 g/l vs 2.07±0.6 g/l). Age, gender, body mass index and HbA1c values were comparable in patients using metformin or not using metformin.
Conclusion
It seems to be that metformin was not regularly prescribed in patients with type 2 diabetes mellitus after insulin initiation. However, a combination of insulin with metformin is indeed associated with better glycemic control and less weight gain than treatment with insulin alone.

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SGLT-2 inhibitors as adjunctive therapy in type 1 diabetes: Short experience from a center

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Background
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors were recently approved as adjunctive treatment for type 1 diabetes (T1D), contributing to better glycemic control, cardiovascular and renal protection. Aim: access the efficacy and safety of these antidiabetic agents in selected T1D patients.
Methods
Evaluation of medical records of T1D patients starting SGLT-2 inhibitors between August 2018 and October 2019.
Results
24 T1D patients (58.3% females, n=14), 41.5±12.32 years, on multiple daily injections (n=23) or insulin pump therapy (IPT; n=1), initiating metformin/dapagliflozin 850/5 mg od (n=16), metformin/dapagliflozin 1000/5 mg od (n=5), and empagliflozin 10 mg od (n=3). Body mass index (BMI) was 27.6±3.6 kg/m^2. Diabetes duration was 17.5±9.95 years, 25% with high blood pressure, 45.8% dyslipidemic, 33.3% had retinopathy, 13% nephropathy, 1 patient neuropathy, and 2 (8.7%) history of coronary heart disease. Mean glycated hemoglobin (HbA1c) was 8.3±0.88%, systolic blood pressure (SBP) 132.0±15.32 mmHg, diastolic blood pressure (DBP) 76.7±12.56 mmHg, serum creatinine 0.7±0.16 mg/dl, glomerular filtration rate (GFR) 110.7±25.5 ml/min. Three (12.5%) patients abandoned therapy in the first 3 months due to side effects (genital infection, diuretic effect, diarrhea). One male stopped the medication temporarily (genital infections that eventually ceased). The patient on IPT suspended SGLT2 inhibitor for difficult compliance on ketone bodies surveillance and desire to keep IPT. No episodes of DKA were reported. 20 patients were followed for 10.1±3.56 months: there was a reduction of 0.7% in HbA1c (8.2±0.94% vs 7.5±0.72%; p<0.001), loss of 3.0±3.19 kg (75.8±13.99 vs 72.8±13.77 kg; P=0.001), improvement in BMI (27.4±3.68 vs 26.4±3.72 kg/m^2; P=0.001), and reduction of 6.8±8.80 IU in total daily dose (TDD) of insulin (n=11; 62.7±22.22 vs 55.9±22.00 IU; P=0.028). Overall reduction occurred in basal insulin dose (total basal dose 31.0±12.35 vs 26.7±12.08 IU; P=0.075), with no statistical significance. Despite overall reduction, the differences were not significant for SBP (P=0.127), DBP (P=0.363), total cholesterol (P=0.132), and LDL cholesterol (P=0.077), probably due to the sample size. Renal function was preserved during the follow-up: no changes in serum creatinine (0.73±0.16 vs 0.73±0.13 mg/dl; P=0.872) and GFR (110.9±25.65 vs 109.6±23.9 ml/min; P=0.741). There were no changes in patient's blood count (hemoglobin 13.7±2.11 vs 13.9±2.22 g/dl, P=0.550; erythrocyte count 4.8±0.51 vs 4.8±0.58, P=0.605).
Conclusion
SGLT-2 inhibitors are an effective adjunct therapy to insulin in T1D, improving glycemic control but also patient's metabolic profile. Careful selection of patients ensures safety of this therapy. Longer follow-up would improve our knowledge of its real-life benefits.

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EP559

Effects of Orthodox fasting on cardiometabolic risk factors: a comparative evaluation between lay fasters and Athonian monks

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Background
Orthodox fasting (OF), a periodical vegetarian subset of the Mediterranean diet, has been shown to exert beneficial effects on human health. Athonian fasting is a pescetarian OF variation, where red meat is restricted throughout the year. Previous studies have examined the OF nutritional synthesis and health impact in general population fasters (GF) and Athonian monks (AM), separately. This is the first study to comparatively evaluate the characteristics and effects of this nutritional pattern between the two populations, with a special interest in cardiometabolic risk factors.
Methods
43 general population male fasters (aged 20–45 years) and 57 age-matched male monks following OF were included in the study. Dietary intake data

were collected in both groups during a restrictive (RD) and a non-restrictive (NRD) day. Nutritional, cardiometabolic and anthropometric parameters were compared between the two cohorts.
Results
AM presented lower daily total caloric intake for both RD (1362.42±84.52 vs 1575.47±285.96 kcal, $P<.001$) and NRD (1571.55±81.07 vs 2137.80±470.84 kcal, p<.001) than GF. They also demonstrated lower Body Mass Index (23.77±3.91 vs 28.92±4.50 kg/m^2, $P<.001$), Body Fat mass (14.57±8.98 vs 24.61±11.18 kg, p=.001) and Homeostatic Model Assessment for Insulin Resistance values (0.98±0.72 vs 2.67±2.19 mmol/l, $P<.001$), compared to GF. Secondary hyperparathyroidism (Parathyroid Hormone concentrations: 116.08±49.74 pg/ml), as a result of profound hypovitaminosis D [25(OH)D: 9.27±5.81 ng/ml], was evident in the AM group.
Conclusions
These findings highlight the unique characteristics of Athonian fasting and its value as a health-promoting diet. The impact of limitation of specific vitamins and minerals during fasting warrants further investigation.

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EP560

Relationship between anxiety-depressive disorder and bone mineral density in diabetic patients with or without diabetic foot

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Purpose
Diabetes mellitus is a complicated disease that is associated with bone mineral density, depression, and anxiety in addition to its association with carbohydrate metabolism. The present study is intended to assess the biochemical measurements, depression and anxiety scores, and bone mineral densities (BMD) of diabetic patients with diabetic foot (DF) compared with those of diabetic patients without DF.
Materials and methods
A total of 37 patients diagnosed with DF and 40 non-DF diabetic patients who were admitted to the Fırat University Hospital Endocrinology and Metabolic Diseases Outpatient Clinic were included in this study according to their Hospital Anxiety Depression Score (HADS). Serum hemoglobin A1c (HbA1c), magnesium (Mg), albumin, urea, creatinine, calcium (Ca), phosphorus (P), parathyroid hormone (PTH), and vitamin D levels were measured along with body mass indexes (BMI). Patients with DF were also assessed according to Wagner's classification. In addition, BMDs were measured from the lumbar and femoral head regions of the patients using dual X-ray absorptiometry.
Result
Depression and anxiety scores were significantly higher in female patients of both groups with and without DF, and the BMD value was also significantly lower in women than in men. Depression and anxiety scores increased as BMI increased in both groups but not to significant levels. BMD results were not significant but trended lower in the DF group. BMI and BMD were found to be positively correlated. Ca, P, and Mg levels related to bone metabolism were significantly lower in the DF group compared with those of the non-DF group.
Conclusion
According to the available data, anxiety, depression, and BMI increase as BMD decreases in DF patients, and this requires a multidisciplinary approach that integrates endocrine and metabolic treatment with psychiatric treatment for these patients.

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EP561

Diabetic neuropathy: Prevalence and risk factors in a type 2 diabetic population

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Introduction
Diabetic neuropathy is a degenerative complication of diabetes mellitus which can be restrictive. The objective of our work is to determine the prevalence of this complication in a type 2 diabetic population as well as its different risk factors
Methods
This is a retrospective study including 100 Tunisian type 2 diabetic patients followed up in the 'C' department at the National Nutrition Institute in Tunis.
Results
The average age of our population was 56.79 years. A female predominance was noted with a sex ratio of 1.9. The average duration of progression of diabetes was 11.28 years. The average HBA1C was 10.83±2.26%. Almost a third of the population had diabetic neuropathy (31%) with no significant difference between the two sexes. The frequency of this complication was significantly correlated with the age and the duration of progression of diabetes ($P=0.025$ and $P=0.002$ respectively). It was best noted in the presence of diabetic retinopathy ($P=0.008$). Diabetic neuropathy was correlated to higher HBA1C and microalbuminuria levels, but this was not significant. It was more common in hypertensive patients who represented more than half of the population. It was more noted in patients with dyslipidemia without this being significant. The uric acid level was significantly higher in the presence of diabetic neuropathy ($P=0.037$). Twenty-three percent of the population was smoking with no statistical relationship to the onset of neuropathy.
Conclusion
As risk factors for diabetic neuropathy, we noted the age, duration of progression of diabetes, poor glycemic control, uricemia, hypertension and dyslipidemia. Being a potential source of invalidity, the screening of the risk factors of this complication and their control are essential.

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EP562

A comparative evaluation of late effects of Orthodox religious fasting vs time restricted eating on metabolic profiles of overweight adults

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Background
Previous research has demonstrated positive effects of Orthodox fasting (OF) and time restricted eating (TRE) on body weight (BW). However, little is known about the late, metabolic effects of the two diets.
Methods
29 overweight adults followed a hypocaloric diet based on OF. A hypocaloric, TRE plan (eating between 08:00 to 16:00 h) was followed by 16 BW-matched participants. Anthropometric, glycemic and inflammation markers and serum lipids were assessed at baseline, at the end of the intervention (7 weeks) and 6 weeks after the cessation of diets (13 weeks).
Results
Both groups demonstrated a decrease in total energy intake at week 13, compared with baseline (OF: 1988±339 vs 2124±315 kcal, $P<0.001$; TRE: 1960±433 vs 2217±350 kcal, $P<0.001$). There was a trend of weight loss in both groups, which was evident at week 7 (TRE: –2.1±1.0; OF: –2.0±0.5 kg, $P<0.001$ from baseline) and remained significant at week 13 (TRE: –2.9±0.7; OF: –2.6±0.3 kg, $P<0.001$ from baseline). In the OF group, lipid concentrations decreased at week 7 and increased at week 13, compared with baseline. Neither group manifested differences in glycemic parameters.

Conclusions
These findings suggest that OF and TRE plans result in significant reductions in BW among overweight adults, which are sustainable even after the cessation of the diets. OF also promotes a decrease in plasma lipid concentrations, which is not evident 6 weeks after its end.

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EP563

Pseudoxanthoma elasticum: About a case report

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Introduction
Pseudoxanthoma elasticum (PXE), a multisystem heritable disorder, is characterized by ectopic mineralization of soft connective tissues. It is an autosomal recessive disorder in which mutations in the ABCC6 gene result in low levels of inorganic pyrophosphate (PPi).
In its classic form, PXE is a late-onset, slowly progressing disease, and the major clinical problems relate to development of vascular complications, including hypertension, intermittent claudication, occasional rupture and bleeding of gastrointestinal blood vessels, and, rarely, early myocardial infarcts and strokes. We report a case of PXE.
Observation
A 18 year-old female patient presented a 1 year history of yellow papules on the lateral sides of the neck. She denied systemic symptoms and family history of similar findings. Her medical history included type 1 diabetes treated with insulin evolving since 11 years. Physical examination revealed white-to-yellowish millimetric non-follicular papules on the lateral aspects of the neck, blood pressure at 120/80 mmHg, heart rate at 76 bpm, peripheral pulse was weak and body mass index (BMI) was 25.84 kg/m^2. The electrocardiogram was normal. In biology: creatinine was correct (45 umol/l), microalbiminuria was negative (6 mg/24 H), total cholesterol: 3.22 mmol/l, HDL-cholesterol: 0.94 mmol/l, trigyceride: 0.62 mmol/l, LDL-cholesterol: 0.77 g/l. Transthoracic heart ultrasound showed myocardial involvement with the presence of intramyocardial calcification. Ophthalmological investigation performed was unremarkable.
Conclusion
The association of PXE and diabetes can be harmful because of cardiovascular complications which can be worsening in a reciprocal way. The cause of PXE remains unclear, and some etiopathogenic theories have been proposed: ultraviolet radiation, intrinsic aging, abnormal elastogenesis, and genetic or inheritable factor.

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EP564

Hyperosmolar Hyperglycaemic State (HHS) and SARS-COV-2 coronavirus- an unusual presentation in a well controlled type 2 diabetic

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Introduction
Hyperglycaemic Hyperosmolar State (HHS) is characterised by Hypovolemia, marked hyperglycaemia, Osmolality of 320 mosmol/kg or more with the absence of acidosis and hyperketonaemia (Ph>7.3, bicarbonate>15 mmol/l). This is a presentation usually found in people with poorly controlled Type 2 Diabetes Mellitus (T2DM). During the current pandemic of COVID-19, there have been atypical and unusual presentations of Diabetic Emergencies, in patients with well controlled Diabetes having inter-current COVID-19 infection.
Case details
We report the case of an elderly gentleman, with a history of T2DM which was adequately controlled solely by Dietary measures. He was admitted with symptoms of feeling generally unwell and was found to be biochemically in HHS. On examination, he was found to be severely dehydrated with no obvious focalising signs of any infection. Biochemically, he was hyperglycaemic, Serum Osmolality of 361(Sodium- 165, Urea- 17.9) and Ketones were 0.1.On the Full Blood Count, the only marker of note was Lymphocytopenia. As an inpatient, he had consistent spikes of temperature and new Oxygen requirements, which raised the suspicion of COVOD-19 infection following which he had a SARS-COV2-RNA swab which was positive. Radiological evidence was indeterminate for COVID-19.
Management
In accordance with the HHS guidelines, the patient was initially treated with IV Fluids. Following this, he was transferred to the Diabetic ward, where he was started on Insulin, due to persistently raised Blood Glucose levels, despite the fluids. He required high doses of Insulin to alleviate his Blood Glucose levels and was subsequently established on twice a day Insulin regime. In view of his symptoms and the acuity of deterioration in his Diabetes control, COVID-19 swabs were sent off, which confirmed inter current Coronavirus infection.
Summary
This case focuses on the atypical effects and implications that COVID-19 can have in the context of Diabetics, for even those who are well controlled. Infection of SARS-CoV-2 in those with diabetes possibly triggers higher stress conditions, with greater release of hyperglycaemic hormones namely Cortisol and Glucagon, thus leading to increased blood glucose levels and abnormal glucose variability. Among different cytokines found significantly higher in patients with diabetes compared to those without, Interleukin-6 (IL-6), may play a more deleterious role in Covid-19 infection. Even in patients whose Diabetes is well controlled, COVID-19 infection can possibly precipitate an inflammatory response and Cytokine storm, thus resulting in a Diabetic emergency to be the presenting feature.

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EP565

Effects of COVID-19 lockdown on physical activity among adults in Tunisia

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Introduction
In order to avoid the spread of the Corona Virus disease, Tunisia has imposed strict confinement measures. The lockdown may change Tunisian's physical activities.
The aim of this study was to evaluate the impact of COVID-19 lockdown on physical activity among adults in Tunisia.
Methods
It was a transversal study conducted from 31th of May to 06th of June 2020. The target audience was adults aged between 18 and 65 years old. Online questionnaire was published and shared via social media. To assess the physical activity before and during the lockdown, surfers were asked to answer anonymously the Ricci-Gagnon self-questionnaire.
Results
A total of 562 provided valid responses to the questionnaire. Women represented 93.4% of the participants. The mean age was 36.96±8.61 years. More than 92% had completed higher levels of education. Almost 15% were smokers. The majority were married (69.4%). The study population was from Great Tunis region in 62.8% of cases.
The mean score of Ricci-Gagnon self-questionnaire was 18±7.2 before the lockdown and 14.4±6.5 during the lockdown (P=<10^{-3}). The decrease of the score was related to gender (–6.2±8.02 among men vs –3.43±7.54 among women; P=0.029). Before the lockdown 60.1%; 38.8% and 1.1%of responders are considered inactive, active and very active, respectively. Home confinement increased significantly the rates of sedentary among adults in Tunisia (74.6% during lockdown vs 60.1% before; P=<10^{-3}). About 31.5%of people were no more motivated to practice sports regularly since gym closure.
Conclusion
Before the COVID-19 confinement, the majority had a sedentary lifestyle. Physical activity was more decreased by lockdown.

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EP566

Comparison of the characteristics of COVID – 19 Patients with and without type 2 diabetes – single center perspective

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Introduction
COVID 19 is now a global pandemic. Oxygen saturation (SpO2), male gender and diabetes have been associated as risk factors for critical care admission, intubation, and prolonged intubation in hospitalised patients. Bacillus Calmette-Guérin (BCG) vaccine may have protective role of against COVID-19
Methods
We retrospectively evaluated inpatient records, of patients admitted over last three months in a public hospital in Northern India to compare attributes and characteristics in COVID-19 patients with and without T2DM. Unpaired t – test, ANOVA and Fisher's exact test was utilised for statistical analysis
Results
We analysed a total of 318 COVID – 19 patients (178 males, 140 female). Mean age of cohort was 42 years (± s.d. 18, minimum 2, maximum 82, 95% CI 40 to 44). There were 47 (14.7%) patients with T2DM (36 males, 11 female) and 271 (85.2%) patients (142 males, 129 females) did not have T2DM (NT2DM). Mean age in T2DM was 54 years (± s.d. 11, 95% CI 51 to 57, min 31, max 76) and in NT2DM was 40 years (± s.d. 18, 95% CI 38 to 42, min 2, max 82); $P<0.0001$. There were 76.6% males in T2DM group as compared to 52.4% males in the NT2DM group (OR 2.97 95% CI 1.46 to 6.13); $P=0.0023$. The mean peripheral capillary oxygen saturation at the time of admission (SpO2) in cohort was 91% (± s.d. 9, 95% CI 90 to 92). Mean SpO2 in T2DM was 89% (± s.d. 7.6, 95% CI 87 to 91, min 65, max 98) and in NT2DM was 91% (± s.d. 7.6, 95% CI 90 to 92, min 45, max 99); $P=0.11$ (ns). Overall, 239 (75.1%) had BCG vaccine. There were 29 (9.12%) T2DM who had BCG vaccination, 210 (66%) NT2DM and had BCG, 18 (5.6%) T2DM- No BCG and 61 (19.1%) NT2DM – No BCG. (OR 0.46, 95% CI 0.24 to 0.9) p = 0.27 (NS). 61.7% (29/47) of T2DM and 77.4% (210/271) of NT2DM had BCG vaccination.
Conclusions
We observed that patients with T2DM were significantly older by 14 years, with a greater number of males in T2DM than in NT2DM. SpO2 was numerically less by 2% in T2DM and with relatively less vaccination coverage. The varied differences in T2DM group would make them more vulnerable to severe COVID-19.

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EP567

Health-related quality of life in children with type 1 diabetes: A multicentric prospective study

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Introduction
Type 1 diabetes mellitus (T1DM) is one of the most common endocrinological chronic diseases in children that may affect the physical and mental health of children by causing a deep upheaval in their life. Children with type 1 diabetes mellitus (T1DM) have to deal with a complex and demanding daily treatment regime which can have a negative impact on the quality of life (QoL) of these patients. The goal of our study was to evaluate the quality of life of school-age children with T1D.
Material and methods
We conducted a multicentric prospective study collecting diabetic children aged 6 to 12 years. We used the PedsQL3.2DM scale translated into Tunisian dialect and which assesses the following items: symptoms of diabetes, barriers and adherence to treatment, anxiety and communication. The scores obtained were scored from 0 to 100 (100 corresponding to a better quality of life).
Results
Our study concerned children followed in 5 different centers. We interviewed 91 children aged 10.1 ± 2 years on average, whose diabetes started at an average age of 6.3 ± 3 years. A female predominance was noted. All the children were in school. Half were hospitalized at least once, and all children received daily insulin injections (1–5 injections/day). The mean score of the children according to the measurement scale used was 68.26 ± 14.31. Multivariate analysis revealed that the improvement in the score was linked to the decrease in HbA1C, the low number of injections and advanced parental age.,df;f
Conclusion
Quality of life assessment is an essential health outcome measure in pediatric medicine it should be an integral part of caring for children with diabetes. Psychological support is often necessary in order to optimize their daily life and their prognosis in the medium and long term.

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EP568

Analysis of diabetic patient's visits to private medical center in the context of reforming of ukrainian medical system

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Diabetes mellitus is a global social and medical problem. In the world, there are 463 million diabetic patients, and in 2045 it is expected to be 700 million (IDF DIABETES ATLAS, Ninth edition 2019). In Ukraine, diabetes affects 7.6% of the Ukrainian population, which is 2.5 million people. According to changes in the public health system, we have separate registration of people with diabetes who receive insulin, but it does not include all diabetic patients. Previous years we used special diabetic register SYNADIAB (2001, Tronko M.D.), but nowadays, in the absence of adequate financing, this project can not answer all epidemiological questions. In the context of reforming medical care, visits to a doctor are registered in the system #helsi.me. The problem is that this information is usually received mainly from governmental clinics and rarely involves private medical centers.
Results
We retrospectively analyzed 522 visits to the endocrinologist in one private medical center in Kyiv to find out the structure of visits (primary/secondary, state of compensation of diabetes, a complication of diabetes, age, and gender of the patients). All information was received from the database of the clinic, and all patients signed an agreement on using their personal information. No personal data (including name and others) was published. Some of the patients visited the clinic out patiently, and endocrinologist consulted others during hospitalization to the in-patient department and the stroke department. Few of them were diagnosed as diabetic patients after severe complications, such as stroke or myocardial infarction. We analyzed visits not only to an endocrinologist, but also results of laboratory tests or instrumental findings, or consultations by other colleagues (including cardiologist, neurologist, ophthalmologist). There was a retrospective observational analysis that was focused on important information about the compensation of diabetes, its complication, and the quality of life. We tried to answer whether our data from the private medical center can be useful for providing a special national diabetic register, which will help us to improve the quality of medical care in the national context. This information is necessary, especially nowadays (COVID-19 in the world, changes in the financing of medical care in our country, etc.).
Conclusion
We propose to recreate a diabetic register for the improvement of communication between different medical facilities.

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EP569

The effectiveness of group training course in the obesity treatment in adult women in the Republic of Belarus

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Background and aims
According to the risk factors study for noncommunicable diseases STEPS 2016, carried out under the auspices of the World Health Organization, in 2016–17 years 60.6% Belarusians had overweight (BMI > 25 kg/m^2); 25.4% had obese (BMI > 30 kg/m^2), and the proportion of women with obesity (30.2%) was 1.5 times higher than men (20.2%). Thus, the project aim was to develop a methodology for group non-drug treatment of overweight and obesity and evaluate the effectiveness.
Materials and methods
Inclusion in the project was based on the results of filling out an online questionnaire (from 11.02 to 25.02), posted on social networks. 44 young women aged 20–45 years (34.5 (29.0–42.0)) with BMI ≥ 25 kg/m^2 were selected. At the first meeting, growth 1.65 (1.57–1.80) m, weight 75.0 (67.2–135.8 kg,

BMI – 29.6 (25.6–35.7) kg/m^2, waist circumference 80 (78–129) cm, fasting glycemia 4.9 (4.4–5.7) mmol/l, total cholesterol 4.2 (3.8–5.7) mmol/l were estimated. The project is joint initiative of the Belarusian Women's Union and Belarusian Public Medical Association 'Endocrinology and Metabolism'.
Results
Using the Dutch Eating Behavior Questionnaire (DEBQ) 59% (26 women) had restrained eating behavior, 45% (20 women) had emotional eating behavior, 41% (18 women) had external eating behavior, any eating disorder – 81% (35 women). The food diary led 91% (40 women) to the second meeting, 56.8% (25 women) to the third. BMI decreased by 7% (became 27.5 (25.2–33.4). In the first three months of work, total weigh became easier by 46 kilograms. A decrease in body weight was noted in 81% (36 women), in 19% (7 people) unchanged. After training course, the proportion of patients with eating disorders decreased to 68% (30 women). A group of dynamic observation was formed, the purpose of which is to maintain optimal body weight and the formation of healthy habits.
Conclusions
A high proportion of people with eating disorders among women with overweight and obesity in the Republic of Belarus is determined. The application of group training meetings is effective in reducing body weight.

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EP570

Neurological characteristics of patients with diabetic nephropathy V st.

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The aim of investigation
To study neurological characteristics of patients with type 1 and type 2 diabetes who received hemodialysis
Material and research methods
We for the period from January, 01.2017 to December, 31, 2017 year 102 patients with type 1 and type 2 diabetes mellitus were examined. Of these, men – 45 (44.1%), women – 57 (55.9%). Average age: men amounted to 57.12 years, women – 58.15 years. 20 of them were urgently received hemodialysis. The research methods included: 1) general clinical (study of endocrine, neurological status, anthropometry 2) instrumental (fundus, visual acuity, ECG, densitometry, Ultrasound of internal organs and dopplerography of the main arteries of the head, etc.), 3) biochemical tests (Hb1AC, glycemic profile, urea, creatinine, lipid spectrum, coagulogram),4) hormonal blood tests (insulin, C-peptide etc.)
Research results
Depending on the degree of diabetic encephalopathy, all observed patients were divided into 3 groups:1 gr – 23 patients with diabetic nephropathy of 4–5 stages with CBI 1 st (chronic brain ischemia); 2 gr. – 45 patients with diabetic nephropathy of 4–5 stages with CBI 2 st; 3 gr. – 34 patients with diabetic nephropathy of stages 4–5 with CBI 3 st.
Analysis of neurological status showed various disorders. Patients of the 1st group had headaches, noise in the head, memory loss, and in the neurostatus the disappearance of surface reflexes, anisoreflexia. Patients of the 2nd group experienced headaches, noise in the head, memory loss, depression, sleep disturbances, attacks of transient ischemic attacks, and the appearance of pathological Babinsky symptoms from 2 sides was characteristic in the neurostatus. In the 3 group of patients, we observed a history of stroke in 5 cases (14.7%), in neurostatus hemiparesis in 5 patients(14.7%), dysarthria – 4 cases (11.7%), pseudo-bulbar syndrome – 6 patients (17.6%), increased muscle tone in spastic and plastic type – 11 patients (32.3%).
Conclusions
1) Among the examined 102 patients, patients with a 2 degree of chronic cerebral ischemia prevailed; 2) Severe neurostatus disorders were detected in patients of group 3.

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EP571

Inaugural diabetic ketosis in iatrogenic cushing syndrome

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Introduction
The main widespread type of diabetes are type 1 and type 2 diabetes, and secondary causes must always be assessed if there is any suspicion.
Cushing Syndrom is one of the main causes of endocrine disorders causing diabetes, though it is rarely revealed by a ketosis.
We herein report the case of inaugural ketosis in a patient with an iatrogenic Cushing Syndrom.
Observation
A 27-year-old man was referred to us for inaugural diabetic ketosis. There is a family history of type 1 diabetes in the brother, and no personal medical history. He reported the cardinal signs of diabetes with weight loss, asthenia, polyuria and polydipsia. Physical examination showed a normal blood pressure, a body mass index of 27.42 kg/m^2, and no signs of neuropathy or complications of diabetes. He had thin skin, purple stretch marks and multiple bruises. The patient was taking 2.25 milligrams of betamethasone daily for four years in order to fain weight, resulting in a Cushing Syndrom with iatrogenic corticotropin deficiency. On complementary exams, there were no signs of infection, the electrocardiogram was normal, the glycated hemoglobin was at 10.7%, kidney and liver testings were normal, and thyroid-stimulating hormone levels were at 2.32 μIU/ml. The ketosis was cured after one injection of ten international Units of fast-acting insulin, and he was put under a basal-bolus injection regimen and 60 milligrams per day of hydrocortisone with gradual tapering.
Discussion
In this patient, the type of diabetes is unclear as the inaugural ketosis is rarely observed in glucocorticoids induced diabetes, and type 1 diabetes is less likely considering the fast response to insulin, and must be excluded first before concluding to an endocrine disorder. For further investiations, testing was realized for Glutamic Acid Decarboxylase 65 and protein tyrosine phosphatase antibodies, the results are still in progress. Follow up on this case and his insulin needs after glucocorticoid tapering and discontinuation will lead to the etiologic diagnosis of diabetes mellitus.

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EP572

'Clinical characteristics of patients with type 1 and type 2 diabetes mellitus who received hemodialysis in 2017 year'

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The aim of investigation
To study clinical characteristics of patients with type 1 and type 2 diabetes who received hemodialysis in 2017 year
Material and research methods
We for the period from January, 01.2017 to December, 31, 2017 year 102 patients with type 1 and type 2 diabetes mellitus were examined. Of these, men – 45 (44.1%), women – 57 (55.9%). Average age: men amounted to 57.12 years, women – 58.15 years. 20 of them were urgently received hemodialysis. The research methods included: 1) general clinical (study of endocrine, neurological status, anthropometry 2) instrumental (fundus, visual acuity, ECG, densitometry, Ultrasound of internal organs and dopplerography of the main arteries of the head, etc.), 3) biochemical tests (Hb1AC, glycemic profile, urea, creatinine, lipid spectrum, coagulogram),4) hormonal blood tests (insulin, C-peptide etc.)
Research results
Depending on the degree of diabetic encephalopathy, all observed patients were divided into 3 groups:1 gr – 23 patients with diabetic nephropathy of 4–5 stages with CBI 1 st (chronic brain ischemia); 2 gr. – 45 patients with diabetic nephropathy of 4–5 stages with CBI 2 st; 3 gr. – 34 patients with diabetic nephropathy of stages 4–5 with CBI 3 st. Analysis of clinical and medical history studies showed that the duration of the disease prevailed in patients of the 3rd group – 22.5 years, while in patients of the 2nd group – 15.6 years, and in patients of the 1st group – 11.7 years. 22 patients were died during year. Stage 5 diabetic nephropathy was detected in all patients
Conclusions
1) Among the examined 102 patients, patients with a 2 degree of chronic cerebral ischemia prevailed; 2) The duration of the disease prevailed in patients of the 3rd group – 22.5 years

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EP573

Pregnancy induced hypertension in women with gestational diabetes mellitus (GDM)

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The aim
To define the prevalence pregnancy induced hypertension (eclampsia, severe preeclampsia, mild preeclampsia, and gestational hypertension) among women with gestational diabetes in Uzbek population.
Material and methods
The epidemiological study involved 1812 pregnant women from 6 pilot regions (Kashkadarya, Samarkand, Fergana, Surkhandarya, Namangan, Khorezm). GDM was screened for the first time among 1812 pregnant women in the period of 20–32 weeks of pregnancy, aged 18–40 years. We extended gestation age beyond the recommended 24–28 weeks to provide flexibility for women who did not exactly remember the date of their last menstruation. Screening included: an anamnesis (presence of risk factors, number of births, etc.), anthropometry (height, weight, calculation of BMI), a study of fasting venous blood glucose and after OGTT (75 g glucose). Women were excluded from the study if they were previously diagnosed with diabetes and/or were taking medications that affect their blood glucose levels.
Results
A total of 196 women were diagnosed as having GDM according to IADPSG diagnostic criteria which resulted in a GDM prevalence of 10.5%. The two groups were similar with respect to BMI, gravidity and parity. The GDM subjects had significantly higher fasting-and 2-h glucose values during OGTT compared to controls. Gestational age at OGTT was similar in the two groups. The frequencies of preterm birth, previous delivery of a macrosomic infant and age ^ 35 years were significantly higher in GDM patients than in controls, whereas a family history of diabetes, the frequencies of prepregnancy overweight, previous unexplained stillbirth were similar in the two groups.
Conclusions
Hypertensive disorders were more frequent in GDM subjects than in controls (19.6% vs. 10.5%).Women with gestational diabetes mellitus were initially thought to have borderline significantly increased risk of preeclampsia (relative risk 1.47; 95% confidence interval 0.92–2.05) and of pregnancy-associated hypertension (relative risk 1.08; 95% confidence interval 0.96–3.22). These findings suggest that women with gestational diabetes mellitus do indeed have an increased risk of preeclampsia.

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EP574

Perception regarding acceptance of telemedicine in urban and suburban population of central india during COVID-19 lockdown

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Introduction
India has a huge population of 1350 million and most of it has a patchy availability of healthcare services, where specialist care is not available at most parts of the country. Telemedicine has been recently approved in India by government of India to be implemented during the COVID-19 lockdown as most of the patients will not be able to have the routine in clinic opd consultations.
Aim and objectives
We tried to see the impact and perception of telemedicine in people of central India as to how they perceive this newer concept, how satisfied they felt with it and how they want to go ahead with it. There are no previous studies of this regard in this population.
Materials and methods
374 subjects from central India who have opted for telemedicine consultation during this COVID-19 lockdown period from 1st April 2020 to 15 may 2020 were surveyed. All the respondents were novel users of telemedicine. responses were recorded and analysed by simple mathematical calculations.
Result
Most of the respondents 54% used Telephonic consultation only as compared to 46% who used online video consultation, highest number of patient 47.5% took consultation for DM, 80.5% respondents were happy with teleconsultation, 66.7% respondents found teleconsultation better during pandemic but 77.2% said they would like to have in clinic consultation once the lockdown eases and 36.8% don't like to pay for teleconsultation.
Conclusion
Telemedicine is not the answer to all the healthcare problems, but it can be very important in addressing a vast number of issues. There is a need to spread awareness about this tech-tool to the common man so that they can avail quality healthcare services. We also need to further study the perception of telemedicine as the lockdown eases and its impact in societies with lower education levels.

Keywords: telemedicine, COVID-19, lockdown, online consultation
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EP575

Clinical manifestations of musculoskeletal complications of acromegaly

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Summary
Objective
To study the clinical manifestations of musculoskeletal complications (MSC) of acromegaly, to improve the early diagnosis of the disease.
Materials and methods
150 patients with acromegaly were examined who were observed at the RSSPMC of Endocrinology during the period from 2000 to 2020. The age of patients ranged from 19 to 76 years and averaged 43±8.6 years. Of these, 65 (43.3%) were men and 85 (56.7%) women. Moreover, the duration of the disease ranged from 1 year to 23 years.
Results
An analysis of the complaints of our patients showed that the most common complaints of deformation of MSC are an increase in the size of the fingers (96.7%), hands (100%) and feet (98.7%), an increase in the nose, lips (93.3%), changes in facial features (86.7%), swelling of the face and hands (85.3%). More than half of the patients complained of pain (in the spine (73.3%) and in the knees – 56%, in the thigh area – 56.7%). All this led to general weakness and reduced ability to work (88%). As the results of the study showed, in more than half of our patients, different MSCs can be detected by X-ray analysis. So, in 92% of patients, deformation of the phalanges of the hands, feet, thickening of the bones of the skull (92.7%) and signs of osteoporosis of the spine (90%) were detected; 80% have expansion of the periarticular space and deformity of the lower jaw, an increase in sinuses (84%) and signs of osteoporosis of the femurs (80.7%).
Conclusions
1. Among the clinical manifestations of complications of the musculoskeletal system in our patients were enlarged hands and feet (100%), swelling of the joints (93.3%), expansion of the distal phalanges (92%), swelling of the face (90.6%), prognathism (80%) and diastema (72%), limited mobility of the knee joints (70%) and polyarthralgia (66%). 2. Radiography, being one of the available methods for the diagnosis of MSC of acromegaly, allowed the detection of deformation of the phalanges of the hands in 92% of patients, feet, thickening of the bones of the skull (92.7%) and signs of osteoporosis of the spine (90%); 80% have expansion of the periarticular space and deformity of the lower jaw, an increase in sinuses (84%) and signs of osteoporosis of the femurs (80.7%).

Keywords: acromegaly, musculoskeletal complications, osteoporosis
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EP576

Challenges in hyponatremia etiology and management in a child with a suprasellar tumour

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Introduction
Hyponatremia is the most common hydroelectrolytic disturbance in clinical practice. Multiple causes exist for its occurrence, being the etiological diagnosis sometimes complex. In patients with suprasellar tumours it is even harder due to several confounding factors. Management of these patients is difficult as it conflicts with chemotherapy-associated hyperhydration protocols. We present a case that exemplifies this.
Clinical case
Four year-old female born in Angola diagnosed with a suprasellar pilomyxoid astrocytoma. She was submitted to a ventriculoperitoneal shunt and started chemotherapy with vinca alkaloids. Due to hypoosmolar hyponatremia, she was first diagnosed with secondary adrenal insufficiency and started therapy with hydrocortisone and, given the persistency, also fludrocortisone. When she was first seen in Endocrine department she was under 30 mg/day of hydrocortisone and 0.075 mg/day of fludrocortisone. She was clinically euvolemic and maintained hypoosmolar hyponatremia (sodium 130 mmol/l; osmolality 258.8 mOsm/kg) with low uric acid concentration and normal renal function. She presented with stage 2 pubic hair, probably due to iatrogenic pubarche. The pituitary axis evaluation was normal (ACTH 23.1 pg/ml; cortisol 15.2 μg/dl – without morning dose of hydrocortisone; TSH 0.75 μUI/ml; free T4 1.44 ng/dl; LH 1 mUI/ml; FSH 6.5 mUI/ml; estradiol 42 pg/ml). She started weaning off hydro and fludrocortisone and a syndrome of inappropriate antidiuretic hormone secretion (SIADH) due to brain tumor and/or vinca alkaloid therapy was suspected. She started hydric restriction and 0.25 g/kg of urea. Sodium levels were difficult to manage but documented as normal whenever the medication was strictly followed. She is now seven years old, Tanner stage 1, her tumor is stacionary in size (55 × 36 mm) under chemotherapy with a third line vinca alkaloide. She still needs medication to control hyponatremia.
Conclusion
The etiology of hyponatremia in this child was particularly challenging. Hyponatremia in this context is difficult to manage. We emphasize the potential complexity of correctly diagnosing and treating these patients.

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EP577

'Neuro-visualization characteristic of the chiasmal-sellar region of the pituitary gland in patients with neuroendocrine diseases'

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The aim of investigation
To study the tomographic characteristic of the chiasmal-sellar region (CSD) in patients with volumetric formations of the hypothalamic-pituitary region.
Material and research methods
We for the period from 2018 to 2020. 34 patients with various pituitary adenomas were examined. Of these, men – 15 (44.1%), women – 19 (55.9%). Average age: men amounted to 37.12 years, women – 38, 15 years. The research methods included: 1) general clinical (study of endocrine, neurological status, anthropometry 2) instrumental (perimetry for all colors, fundus, visual acuity, ECG, densitometry, CT/MRI of the Turkish saddle, etc.), 3) hormonal blood tests (STH, IGF-1, LH, FSH, PRL, TSH, ACTH, prolactin, etc.)
Research results
Among the 34 patients examined, various formations of the Sellar region were identified: non-functional pituitary adenoma (NFPA) – 21 patients, prolactinoma – 3, Itsenko-Cushing's disease – 4, craniopharyngoma –2, acromegaly –4. Depending on the size of the pituitary adenoma, the following pituitary changes were found on CT/MRI: microadenomas (<10 mm) – 2 patients (5.8%), mesoadenomas (11–20 mm) – 3 patients (8.8%), macroadenomas (up to 30 mm) – 4 patients (11.6%), giant – (more than 30 mm) – 25 patients (73.5%) Distribution of patients according to topographic anatomical classification of the growth side of the pituitary adenoma B. Kadashev (2007) showed that the most frequently observed pituitary adenomas with endosuprasellar growth – 13 bx (38.2%), with infracellular growth – 2 (5.8%), with laterosellar growth – 3 (8.8%), with an antesellar growth of –1 (2.9%), with a retrocellular growth – 1 (2.9%), with a total growth option – 14 bx (41.1%).
Conclusions
1) Among the examined 34 patients with volumetric formations of the sellar region, patients with giant pituitary adenomas (more than 3 cm) predominated – 25 cases (73.5%). 2) The most common endo-suprasellar growth of the neoplasm was 13 cases (38.2%).

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EP578

Complete growth hormone deficiency associated with solitary median maxillary central incisor syndrome (SMMCI)

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Introduction
Solitary median maxillary central incisor syndrome (SMMCI) is a complex disorder consisting of multiple, mainly midline defects of development resulting from unknown factors and an uncertain etiology. Its incidence is estimated at 1/50.000.
Material and methods
We report 2 cases of patients with SMMCI associated with GH isolated deficiency in one case and multiple pituitary hormone deficiency in the other one.
Case 1
A 4-year-old girl with no significant medical history consulted for growth retardation at –3.5 s.d. She had a particular physionomy with blond hair, fair skin (contrasting with the skin tone of the parents), baby face and a single maxillary median central incisor. Psycho-motor development was normal. Hormonal investigations concluded to a complete GH deficiency, a central hypothyroidism and a central corticotropic deficit. Hypothalamic MRI showed a pituitary stalk interruption syndrome without any other cerebral anomaly. No other malformation (cardiac, renal, vertebral) was found. She was treated by growth hormone, L-thyroxine and hydrocortisone with satisfying heigt gain and improvement of general condition.
Case 2
The second observation is about a 7-year-old girl with a complete and isolated GH deficiency discovered at the age of 3. She was receiving GH regularly with good results. She had the same particular physionomy than the first girl : blond hair and baby face. This made us re-examine her, so we found also the same dentar anomaly : a solitary median maxillary central incisor. Notice, the parents didn't pay attention to this anomaly in the two cases.
Conclusion
The SMMCI is a rare condition that may be associated with midline anomalies, hypopituitarism, holoprosencephaly and other visceral malformations. It constitues also an eshtetic problem that requires interdisciplinary intervention, generally after the eruption of the permanent teeth.

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EP579

Successful pregnancy after pituitary surgery: A case report

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Background
current studies reported that pregnancy in women with hypopituitarism is rare and several obestristics and endocrinologic complications must resolve for successful pregnancy among these women. Here we report one woman with hypopituitarism who became pregnant after hormonal replacement therapy.
Method
A therapeutic strategy for 34 years old pregnant women as known case of pituitary surgery and completed pan hypopituitarism was designed. We

performed one hormonal replacement strategies including HCG, HMG, prednisone and levothyroxine hormones and after that, we stimulate ovulation process with growth hormone.
Results
After therapeutic time, our patient could achieve a successful pregnancy and delivered her son in due course.
Conclusion
Pregnancy is possible for females suffering from hypopituitarism due to total hypophysectomy by an individualized therapeutic strategy using growth hormone for ovulation stimulation.
Keywords: hypopituitarism; total hypophysectomy; pregnancy
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EP580

Internet search engine queries on abortion and miscarriage peak after a query on missing a dose of oral contraceptive

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Objective
Oral Contraceptives (OCs) are a unique chronic medication where a slip of memory may be experienced as a threat that could change the life course of a person. Internet search engine queries provide a unique access to concerns and information gaps in a large number of internet users. We sought to quantitate internet search engine queries on missing one or more doses of an OC and subsequent queries on emergency contraception, abortion and miscarriage. We also quantified their rate of reporting a pregnancy timed to the cycle of missing an OC.
Study design
We extracted all Bing English-language queries submitted in the US during 2018 mentioning a missed OC, and further queries by the same users on miscarriage, abortion, emergency contraceptives and week of pregnancy and analyzed temporal trends and query frequency in different age groups.
Results
We identified 26.395 Bing users in the US who searched Bing on missing OC pills and the subfraction who queried about miscarriage, abortion, emergency contraceptive and week of pregnancy after their initial missed OC query. Users under the age of 30 who asked about forgetting an OC dose were more likely to ask about abortion (× 1.5) and emergency contraception (× 1.7) (P-value = 0.00 006 and 0.00 001, respectively), while at ages 30–34 queries about pregnancy (× 2.1) and miscarriage (× 5.4) were more likely (P-value = 0.000002 and 0.000004, respectively).
Conclusion(s)
A large number of women ask about missing a dose of OC, either because they have not have received sufficient information from their healthcare providers or because they preferred to obtain information online. Queries about abortion and miscarriage peaking in subsequent days may indicate a common worry of possible pregnancy.
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EP581

Oral antioxidants improve sperm motility, sperm concentration and reduce oxidative stress in males with oligoasthenozoospermia

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Male infertility is a worldwide healthcare issue, which has driven developed countries to take the necessary steps in detecting and treating the problem. While transition countries such as North Macedonia and most of the surrounding states belonging to the Western Balkans, usually blame the female partner for infertility, thus male factor is underestimated. The term 'milieu intérieur' means also a perfect equilibrium between reactive oxygen species (ROS) and antioxidant capacity (AC), crucial for physio-pathological effects on sperm maturation and capacitation, but not only. Oral antioxidants have been shown to diminish oxidative stress (OS) and improve semen parameters, mostly sperm motility and concentration. For this purposes we enrolled 37 infertile males. First semen sample was collected at the time of enrollment in the study. From this 0.5 ml was used for standard semen analysis, while 1.2 ml for evaluating OS parameters such as malonedialdehyde (MDA) and protein carbonyl (PC). A second sample was collected after 6 months of antioxidant treatment. Mean, Standard Deviation, the Pearson Correlation and paired student t-test (since normal distribution was tested by Shapiro-Wilk test) were used for statistical analyses. Levels of MDA are negatively correlated with sperm motility (r = –0.53) and sperm concentration (r = –0.19), so show and levels of PC with sperm motility (r = –0.36) and sperm concentration (r = –0.12). After six months of treatment the semen parameters such as concentration and motility, improve significantly (P < 0.001), MDA also decreases significantly (P < 0.001), PC was also lower after the treatment, but was not statistically significant (P = 0.0554). Antioxidants improve semen parameters in terms of concentration and motility, and dramatically reduced the oxidative stress markers. Considering cost-efficiency of oral antioxidant administration to infertile men, the potential advantages that such treatment offers cannot be ignored. Our suggestion is that Antioxidants should be used on a routine basis in cases of idiopathic male infertility. Anyway, further randomized controlled trial on larger sample size for standardization of doses and duration of supplementation are needed.
Keywords: male infertility, semen parameters, malonedialdehyde, protein carbonyl, antioxidants.
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EP582

Graves' disease following Hashimoto's thyroiditis. Case report

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Hyperthyroidism in Graves' disease (GD) is caused by thyroid-stimulating autoantibodies to the TSH receptor. Hypothyroidism in Hashimoto's thyroiditis (HT) is associated with thyroid peroxidase and thyroglobulin autoantibodies. Transformation of HT to GD has been rarely reported. We report a woman with history of HT, who then developed GD.
Case presentation
A 50-year-old female with a past history of hypothyroidism due to HT treated with Levothyroxine from 2016 to 2018, presented in March 2020 with palpitations, dyspnea on slightest effort and dizziness. Thyroid gland was symmetrically normal, without any bruit. There were no ocular manifestations. Initial thyroid function tests revealed: TSH: < 001 mUI/l (0.27–4.20), FT4:37 pmol/l (12–22), TPO antibodies: 216 UI/ml (<34), TG antibodies: 202 UI/ml (< 34); TSH receptor antibodies: 10 U/l (< 1). Thyroid ultrasonography showed a multinodular gland with a nodule of 17 mm located in the left lobe. 99 m Tc pertechnetate scan showed a normal sized gland with increase uptake of radiocontrast, typical image of GD.
Comment
HT and GD represent the main two types of autoimmune thyroid disease. The conversion to GD from HT is a rare phenomenon which needs further immunological and genetic studies to explain this unusual autoimmune disorder and the time between hypothyroidism and the occurrence of hyperthyroidism. In our case, hyperthyroidism appeared 4 years after hypothyroidism due to HT.
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EP583

Myxedema: How a lack of follow up can lead to a medical emergency

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Myxedema coma is a potentially lethal presentation of severe hypothyroidism. It is a rare condition in the Western society. We present a 72-year-old woman with a myxedema coma precipitated by a urinary tract infection. The patient was admitted to the emergency ward in a subcomatose state featuring hypothermia, hypotension, bradycardia and hypoxia. Diagnosis of myxedema by the attending Emergency Physician was suggested based on clinical presentation. The consulting endocrinologist questioned the diagnosis due to the lack of thyroid related disease at initial review of her medical history and because of its rare incidence. Thyroid tests confirmed the diagnosis of myxedema and subsequent treatment with levothyroxine and liothyronine intravenously resulted in a rapid amelioration of the patient's physical and mental state. During the patient's stay in the hospital it became clear that she had previously been on radioactive iodine therapy for Graves' disease, but that follow-up had been neglected. The case presented here highlights the importance of knowledge of low incidence endocrine disease in the emergency department. Patient who undergo treatment with radio-active iodine should be actively encouraged and reminded to follow up the effects of the treatment. This statement is of particular importance in the current COVID-19 lock down period. Patients are scared to pursue their regular follow-up. Tele-consultations and video consultations may be an alternative to face to face consultations in order to avoid loss to follow-up and detect timely overt thyroid dysfunction.

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EP584

Acute thyroiditis treated with Levofloxacin in overall healthy young woman – after subacute thyroiditis

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Introduction
Acute thyroiditis is rare disease and it affects mainly immunocompromised patients. First line antibiotics for treatment are Ampicillin and Cephalosporin.
Case report
30 y/o woman presented with neck pain and according clinical-laboratory tests was diagnosed with subacute thyroiditis.

- TSH-0.018(0.350–4.940 μIU/ml);
- FT4–32, 32 (9, 01–19, 05 pmol/l)
- CRP-151.25 (<5 mg/l)
- WBC-10.81(3.50–10.00) 10^9/l
- E.S.R 48(<20 mm/h)
- Thyroid ultrasonography- Left lobe –10.7 cm^3, right lobe 10, 9 cm^3. With autoimmune thyroid disease signs.

Treatment with methylprednisolone 16 mg was started and after releasing of pain, gradually lowered. After withdrawal of hormone in about 8 weeks, patient's pain returned. NSAID was initiated, but treatment did not help and patient began to take again methylprednisolone. After second withdrawal of hormone in 6 weeks, more acute pain came back, with swollen left side of neck, dysphagia and dysphonia. Patient decided to take 4 mg methylprednisolone for 2 days, which did not help and she came for evaluation. Thyroid ultrasonography – Left lobe enlarged –14.6 cm^3, right lobe reduced-6.7 cm^3. In left lobe was infiltrate-like appearance lesion.

- TSH-0, 39 (0.27–4.2 μIU/Ml)
- WBC- 11.87 (4.4–11.3 10^3/mm^3)
- Neutrophils% 85.3%(50–75)
- ESR 3 mm/hr<25ESR.

Patient refused to take additional tests- CT and FNA, due to financial reasons. Treatment for acute thyroiditis with Amoxicillin/clavulanic acid 2000 mg daily was started and methylprednisolone stopped. Patient had-allergic rash and itching on face. She remembered, that she had previously allergy on cephalosporin. Because of that Amoxicillin was replaced with Levofloxacin 500 mg and after 1 week patient presented without symptoms.

- WBC-8.63 10^3/mm^(3 4.4–11.3)
- Neutrophils% 67.6%(50–75)
- ESR 7 mm/hr<25ESR
- Thyroid ultrasonography-left lobe was reduced in size twice.

We continued treatment for 1 more week and patient was fully recovered. After 2 months she reports to feel great.
Conclusions
Notwithstanding, that we had limited diagnostic resources and we did not know real pathogen, after good result on antibacterial therapy we can confirm, it was acute thyroiditis. Was it due to glucocorticoids, was it acute thyroiditis from beginning, or some other anatomic reason – we could not find out. It is unusual case, because of patient's young age and overall health. Also it is interesting, because Fluoroquinolone is not widely used in acute thyroiditis and we can suggest it as an effective treatment option.

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EP585

Alopecia universalis as clinical manifestation of hashimoto's thyroiditis: A case report

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Background
Thyroid hormone has an important role for skin growth and development. Alopecia is one of the clinical feature of autoimmune hypothyroidism or systemic autoimmune disease
Case Illustration
A 18-year-old Indonesian woman presented with alopecia universalis. It started with a patchy hair loss which then progress to all of her body. At the age of 15 she had complaints of neck enlargement, palpitation, weight loss, and heat intolerance. Physical examination revealed alopecia universalis and diffuse thyroid goiter. She had high TSHs level and positive TPO-Ab. Thyroid ultrasound characteristics were in concordance with thyroiditis. She was then diagnosed with Hashimoto's thyroiditis and given low dose levothyroxine (LT4), but without any improvement in the alopecia. Screening for other systemic autoimmune disease yielded negative results. She had also toxoplasmosis and has already been given full treatment course.
Discussion
Alopecia areata (AA) is an organ-specific auto-immune disease with genetic predisposition, environmental trigger such as infection, and associated with increased overall risk of autoimmune thyroid disease (TAI) especially those with alopecia universalis (AU). Thyroid autoantibodies were found in AU patients and seem to dysregulate TSH secretion and inflammatory state could mediate its clinical manifestation. The standard treatment of LT4 leads to TSH suppression and reduction of exaggerated inflammatory response in thyroid gland, skin, and decreasing TPO-Ab level.
Conclusions
This indicates the necessity screening for thyroid abnormalities, thyroid autoantibody, and further systemic autoimmune in patients with AU, which is of benefit for early diagnosis and treatment.
Keywords: alopecia areata, alopecia universalis, autoimmune thyroid disease, hashimoto's thyroiditis

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EP586

Hypoparathyroidism incidence in patients operated on papillary thyroid carcinoma — are there any changes in a 20 year time-lapse?

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Introduction
Today, thyroid papillary cancer remains to be the most frequent diagnosed malignancy. Despite highly positive outcomes, treatment protocol still requires surgical intervention, which, in turn often affects not only thyroid and regional lymph nodes, but also recurrent nerve and parathyroid glands. The aim of our study was to compare the metabolic compensation of calcium and thyroid metabolism improvement in patients operated on thyroid cancer recently and 20 years ago.

Material and methods
We have examined two groups of patients (in total 104 men and women with the age of 21 to 43 years old at the moment of operation) treated on highly differentiated thyroid carcinoma in different time periods (1998–2000 and 2018–2029). The first one, analyzed retrospectively, consisted of 44 patients aged 22.16±7.51at the moment of operation, the second one recently selected included 60 patients with mean age 22.16±7.5 years. Both groups did not differ significantly by the age at the moment of operation, as well as by staging – all were marked as stage 2 by pTNM. Daily prescribed amount of levothyroxin was recorded. Tests for TSH, FT4, TG, Parathormone were made using ELISA-DRG (USA) kits and serum calcium levels were estimated on Cormay-Diana biochemical analyzer (Poland).
Results
As a result, comparing two groups we have seen no significant difference in FT4 levels, though significant decrease in mean TSH levels was observed in between groups (0.6420±0.74 mUI/l in group 1 vs 0.3275±0.62 mUI/l) ($P<0.05$) on the almost similar amounts of thyroxin intake 160.14±28.89 vs 153.95±31.21 mg/day respectively, showing significant improvement in compliance and target TSH suppression levels achievement over time. As for the calcium levels – they have also significantly improved over the time of surgical experience – 1.97±0.17 in group 1 vs 2.37±0.12 in group 2 ($P<0.05$) – two decades later. Alongside with the positive shifts – a worrying difference in TG levels was determined –1.91±3.30 ng/ml vs 2.49±3.96 ng/ml ($P=0.03$) That can be explained either by different reagent sensitivity or higher relapse tendency in more sparing surgical techniques.
Conclusion
Improvement of surgical techniques and reduction of postoperative hypoparathyroidism is obvious, but still the minimally invasive approach requires more clinical observation and follow up.

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EP587

RHO gene polymorphisms in patients with Graves' disease

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Graves' disease (GD) is an organ-specific autoimmune disorder of the thyroid due to the presence of circulating anti-thyroid-stimulating-hormone receptor stimulating autoantibodies that lead to hyperthyroidism. Involvement of the genetic variants of *RHO* genes in GD has not been examined yet. Therefore, the aim of this study was to investigate possible associations between RHO gene polymorphisms and GD in a Turkish population. A total of 128 patients with GD and 163 healthy control subjects were included to this study. Genomic DNA was extracted from whole peripheral blood samples and analyzed using the dynamic array system (Fluidigm, South San Francisco, CA, USA). The Chi-square or Fisher's exact tests were used for calculation of the differences in frequencies. The Bonferroni correction for multiple testing was used for polymorphism studies, and $P<0.0071$ (0.05/7) was considered statistically significant. We investigated 7 *RHO* gene polymorphisms. Neither genotype distributions nor the allele frequencies for the *RHOA* rs6784820, *RHOA* rs974495, *RHOA* rs2177268, *RHOC* rs11102522, *RHOD* rs2282502 (Asp88 Glu), *RHOD* rs34270544 (Arg144 Gln), and *RND3 (RHOE)* rs816890 polymorphisms showed a significant association between the groups. This study showed for the first time that there were no associations between studied *RHO* gene polymorphisms and the risk of developing GD in the Turkish population.
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Table 1 The genotype and allele distrubition of *RHO* gene polymorphisms in Graves patients and control group.

Gen/SNP	Genotype/ Allel	Control	*n**	Patient	*n**	*P*
RHOA	AA/AG/GG	65/63/30	158	56/38/28	122	0.3109
rs6784820	A/G	193/123		150/94		0.9930
RHOA	CC/CT/TT	87/54/20	161	84/26/18	128	0.0435
rs974495	C/T	228/94		194/62		0.2136
RHOA	TT/TA/AA	89/33/41	163	80/17/29	126	0.2267
rs2177268	T/A	211/115		177/75		0.1901
RHOC	AA/AG/GG	89/43/23	155	71/23/12	106	0.2968
rs11102522	A/G	221/89		165/47		0.1163
RHOD	GG/GA/AA	66/58/37	161	54/39/29	122	0.7684
rs2282502 (Asp88 Glu)	G/A	190/132		147/97		0.8328
RHOD	CC/CT/TT	157/4/0	161	126/2/0	128	0.6966
rs34270544 (Arg144 Gln)	C/T	318/4		254/2		0.6981
RND3 (RHOE)	CC/CT/TT	153/9/0	162	119/8/0	127	0.8061
rs816890	C/T	315/9		246/8		0.8088

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EP588

Amiodarone induced thyroid disorders – would you miss them?

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Introduction
Amiodarone is a well-established class III antiarrhythmic drug used in the treatment of arrhythmias and atrial fibrillation.
Case Report
History
A 68 year old gentleman who has background history of persistent Atrial fibrillation, dilated cardiomyopathy, took digoxin 125 mg, bisoprolol 2.5 mg and warfarin 2 mg, simvastatin 40 mg, Ramipril 10 mg. Digoxin was discontinued due to the nocturnal pauses, bradycardia on 24 hour holter and Aamiodarone 200 mg was started on April 2015. Following four months commencement of Amiodarone, he developed nausea, palpitation, fatigue, unintentional weight loss and found to have thyrotoxicosis. No iodine-containing contrast agents had been recently administered and family history was negative for thyroid disorders.
Diagnosis
Amiodarone induced thyroiditis [AIT] was made. TSH<0.01 [0.35–5.50 mu/l], Free T4–30 [10–19.8 pmol/l], TSH receptor Antibody –negative, TPO antibody negative. Routine blood tests are unremarkable.
Treatment and Follow up
Amiodarone was stopped and carbimazole was started. His thyroid function test back to baseline, clinically and biochemically euthyroid after two years of treatement.
Discussion
A diagnosis of AIT can be considered at any time in a patient who develops clinical signs of thyrotoxicosis after taking amiodarone. The main mechanism is iodine-induced hyperthyroidism (type 1 AIT), a form of Jod Basedow, or destructive thyroiditis (type 2 AIT), caused by amiodarone itself and its high iodine content. The risk of hyperthyroidism also increases with increased dosage. The effects of amiodarone on the thyroid can be seen as early as a few weeks after startingtreatment and or up to several months after its discontinuation as Amiodarone is lipophilic and has a long half-life in the body.
Conclusion
Patients with cardiac disease receiving amiodarone treatment should be monitored for signs of thyroid dysfunction, which often manifest as a reappearance of the underlying cardiac disease state. Because thyroid dysfunction is relatively common in amiodarone therapy,all patients should have free thyroxine and thyroid-stimulating hormone (TSH) levels measured before starting therapy, at three- month intervals during treatment and for at least one year after the amiodarone is discontinued.

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EP589

Serious progressive risk of Basedow's disease: Thyroid storm

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Introduction
Thyroid storm is an acute exacerbation of hyperthyroidism, responsible for significant mortality despite treatment.

Case report
We report the observation of a 43-year-old diabetic patient with basedow's disease with poor therapeutic adherence; admitted for convulsions and loss of consciousness. The diagnosis of acute thyroid storm on drop out of treatment was mentioned, in front of the detection of peripheral hyperthyroidism with low TSH; T4 at 67.75 pmol/l, T3 at 45 pmol/l, hepatic cytolysis and high creatine phosphokinase. Other clinical parameters included bilateral exophthalmos, vascular goiter, tachycardia at 180 beats/minute, dehydration and hyperthermia. Management consisted on intubation-ventilation, re-administration of carbimazole 50 mg and propranolol 60 mg, with bolus of corticosteroid therapy and rehydration. The patient died within 24 hours despite symptomatic intensive care measures.
Discussion/Conclusion
The thyroid storm is a rare and potentially fatal entity. Low socio-economic backgrounds promote its occurrence. The main difficulty is recognizing its varied presentations, and offering appropriate treatment when the doctor faces a failure, or against contraindications of conventional therapy.

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