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Betimi i Hipokratit

Në çastin kur po hy në radhët e anëtarëve të profesionit mjekësor premtoj solemnisht se jetën time do ta vë në shërbim të humanitetit. Ndaj mësuesve do ta ruaj mirënjohjen dhe respektin e duhur. Profesionin tim do ta ushtroj me ndërgjegje e me dinjitet. Shëndeti i pacientit tim do të jetë brenga ime më e madhe. Do t'i respektoj e do t'i ruaj fshehtësitë e atij që do të më rrëfehet. Do ta ruaj me të gjitha forcat e mia nderin e traditës fisnike të profesionit të mjekësisë.

Kolegët e mi do t'i konsideroj si vëllezër të mi.

Në ushtrimin e profesionit ndaj të sëmurit tek unë nuk do të ndikojë përkatësia e besimit, e nacionalitetit, e racës, e politikës, apo përkatësia klasore. Që nga fillimi do ta ruaj jetën e njeriut në mënyrë apsolute. As në kushtet e kërcënimit nuk do të lejoj të keqpërdoren njohuritë e mia mjekësore që do të ishin në kundërshtim me ligjet e humanitetit. Këtë premtim po e jap në mënyrë solemne e të lirë, duke u mbështetur në nderin tim personal.

The Oath of Hippocrates

Upon having conferred on me the high calling of physician and entering medical practice, I do solemnly pledge myself to consecrate my life to the service of humanity. I will give my teachers the respect and gratitude which is their due. I will practice my profession with conscience and dignity. The health of my patient will be my first consideration. I will respect the secrets which are confided in me, even after the patient has died. I will maintain by all the means in my power, the honor and the noble traditions of the medical profession.

My colleagues will be my brothers.

I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity. I make these promises solemnly, freely and upon my honor

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ABSTRACT

Objective: The aim of our study was to evaluate whether autologous Platelet-Rich Plasma (PRP) injected in the ovarian cortex has therapeutic potency in restoring ovarian function in poor ovarian responders (PORs) after one-month therapy. PRP is beginning to be used in the treatment of ovarian infertility with a possible explanation for its role in improving the follicular microenvironment as well as the influence of growth factors on ovarian stem cells in postnatal oogenesis. Methods: This prospective randomized study included women who contacted the department of IVF in the period from 2017-2018. Women were selected according to the ESHRE consensus on the definition of PORs. A total of 30 women were divided in two groups according to the patient choice: ovarian PRP injection (15 patients) or no intervention (15). PRP was prepared by Regen ACR®-C Kit according to the manufacturer's guidelines. Approximately 3-5 ml of the PRP was injected in ovarian cortex using transvaginal ultrasound guidance. The serum concentration of FSH, LH, estradiol and AMH were determined before the treatment and day-3 of first menstrual cycle after treatment in order to monitor ovarian function. Results: After PRP treatment, the women had significant improvement in ovarian reserve. AMH level in serum was significantly increased, $p<0,05$ ($p=0,02$), FSH level significantly decreased, $p<0,01$($p=0,003$) and number of antral follicles after applying the PRP significantly increased, $p<0,001$ ($p=0,0007$). Conclusions. One-month therapy with PRP has the potency of significantly recovering ovarian function both in its hormonal and follicular development abilities.

Key words: poor ovarian reserves, platelet-rich plasma, Growth Factors

INTRODUCTION

Due to remarks of more authors where the use of PRP improves the function of the target organ, it starts an enthusiastic use of PRP in patients with ovarian insufficiency (1). A possible explanation is the probability of improving the follicular microenvironment as well as the influence of growth factors on ovarian stem cells in postnatal oogenesis. Receptors for growth factors presented on granulose cells confirming their association with the activation process of the primordial follicles. The Growth Factors (GFs) contained in platelet alpha granules are a major part of the PRP. They induce, through appropriate transmembrane receptors in target cells, a whole range of intracellular processes leading to proliferation, differentiation, matrix formation, osteoid production, collagen synthesis, haemostasis, and everything that leads to tissue recovery and regeneration. It is noted, that the mitogen effects of PRP are only limited to augmentation of the normal healing process and is theoretically not mutagenic, as the GFs released do not enter the cell or its nucleus, but only bind to the membrane receptors and induce signal transduction

mechanisms (2).

Oogenesis is the most significant function of the ovarian tissue. For a long time, it was believed that a woman was born with a certain reproductive potential. This dogma has been challenged by evidence supporting postnatal oogenesis in mammals (3). Reports demonstrating formation of new oocytes from newly discovered germline stem cells, referred to as oogonial stem cells (OSCs), has opened new avenues for treatment of female infertility (4). In this context, Tilly's latest review discusses a new concept of how oocyte and their precursor cells can be metabolically altered in order to maintain or increase ovarian function and fertility in a woman. However, if it can be shown that human OSCs are possible precursors of oocytes capable of further fertilization, then they have a potentially high value in the treatment of fertility dependent on aging (5). In addition, it is assumed then OSCs are necessary in the process of haemostasis, regeneration and protecting the integrity of the ovarian tissue. Namely, on the surface single-layer epithelium, "injury" is caused with each ovulation, monthly, and followed by local tissue repair (6).

MATERIALS AND METHODS

The study was approved by the local Ethnics Committee and the Institutional Review Board, and each patient included in the study signed an informed written consent. The study included PORs who meet at least two of the following three Bologna criteria, published by the European Society of Human Reproduction and Embryology (ESHRE) in 2011. They had normal hysteroscopy and their partners had a normal semen analysis (7). The exclusion criteria were ovarian insufficiency due to gonadal dysgenesis and chromosomal abnormalities, immunoglobulin A deficiency, large surgical repairs of pelvic floor leading to the creation of severe pelvic adhesions, the use of anticoagulants, psychotropic medicaments, psychiatric disorders, carcinomas or a history of chronic pelvic pain (8). Women with present infection, haemoglobin lower than 11g/L or platelets lower than 150x10^3/µL were excluded from study (9). In our study, we used a Regen PRP system, (Regen Laboratory, Mont-sur-Lausanne, Switzerland) (10). PRP was prepared according to the manufacturer's guidelines. In the last step the volume immediately above the erythrocyte layer was collected. Calcium gluconate was used as an activator. After activation, in a period less than 2 min, approximately 3-5 ml of the PRP was injected into the ovaries under transvaginal ultrasound guidance. Intervention was made under propofol intravenous anesthesia following a protocol set by our IVF department. We used a 30 cm single lumen 17G aspiration needles (COOK / Australia). We assessed the PRP benefits through the values of AMH, FSH, estradiol, and AFC. The serum concentration of FSH, estradiol, and AMH was determined before the treatment and day-3 of the first menstrual cycle after treatment to monitor ovarian function.

STATISTICAL ANALYSIS

Data analysis is performed in a Statistic program 7.1 for Windows and SPSS Statistics 23.0. For normal distributed data, mean and standard deviation were used. Comparisons across means were evaluated by paired two-tailed Students t-test. The factors with a P-value of <0.1 in the univariate analysis were included in the logistic model. A P-value of <0.05 was considered statistically significant.

RESULTS

In this study demographic characteristic (age, BMI, infertility duration) and baseline ovarian reserve markers (FSH, AMH, AFC) were similar between the two groups. For H = 3.83 and p> 0.05 (p = 0.15), there was no significant difference in FSH value between the two groups (before intraovarian PRP injection). Namely, the FSH in the group later treated with platelet-rich plasma (PRP) was 17.27 ± 5, 29 IU / L, and in the control group of patients with no intervention was17.64 ± 6.69 IU / L. The value of AMH in the control group, 0.56 ± 0.31 ng/ml for p> 0.05, (p = 0.19) was insignificantly higher than the value of AMH in the study group (before intraovarian PRP injection) 0.35 ± 0.19 ng / ml. For H = 0.96 and p> 0.05 (p = 0.62) there was no significant difference in the number of antral follicles between the study group, before intraovarian administration of PRP, (4.53 ± 0.99) and the control group of patients without intervention (4.53 ± 1.06).

The mean value of platelet concentration was 226,27±82,80/10^{3}L. We evaluate day-3 baseline ovarian values of AMH, FSH, and AFC in the cycle before intraovarian cortical PRP injection and in 41±18 days after PRP. After one treatment with PRP, the women in group I had significant improvements in ovarian reserve (table 1 and 2). AMH level in serum was significantly increased, p<0,05 (p=0,02), and FSH level significantly decreased, p<0,01(p=0,003). In our study we noticed an increased

number of antral follicles after applying the PRP, p<0,001 (p=0,0007). There is no change in the control group.

Table 1. FSH values in group I before & after intraovarian PRP injection

Variable	Mean	Std. Dv.	N	Diff.	Std. Dv. Diff.	t	df	p
FSH (before intraovarian PRP injection)	17,27	5,29						
FSH (after intraovarian PRP injection)	12,38	4,26	15	4,89	5,29	3,58	14	0,003

Table 2. Differences between AMH and antral follicular counts in group I before & after intraovarian PRP injection

Pair of Variables	Valid	T	Z	p-level
antral follicular counts before & after PRP injection	15	0,00	3,41	0,0007
AMH before & after PRP injection	15	16,00	2,29	0,02

We can notice that the PRP method objectively has the potential of recovering ovarian function and increases the chances of clinical pregnancy in PORs. After treatment with PRP, AMH level in serum was significantly increased, p<0,05 (p=0,02), and FSH level significantly decreased, p<0,01(p=0,003). In our study we noticed an increased number of antral follicles after applying the PRP, p<0,001 (p=0,0007). It seems this fact is achieved mostly by the paracrine effects of Growth Factors contained in platelet alpha granules as a major part of PRP.

A further analysis was carried out to identify factors that could correlate or predict the response of the PRP injection in ovarian tissue. We took into account the previous investigations carried out by E. Scott Sills but our tests were not significant at the 95% confidence level. Further analysis was performed to identify factors which might correlate the platelet count in the PRP with the values of FSH, AMH, estradiol and total AFC post-PRP. None of the tests presented statistical significance.

DISCUSSION

The use of PRP in reproductive medicine was first reported in 2017 by Pantos at a medical conference at ESHRE (1). During the following year the next pilot study was published. This pilot study was focused on intraovarian injection of autologous platelet-rich plasma before in vitro fertilization (11). It remains essential to understand the physiological basis of the aging of the ovaries in order to interpret the mechanisms of action. With the use of platelet-derived growth factors (PDGFs), dysfunctional ovarian tissue is believed to be supplied with essential factors necessary for ovarian regeneration. In this context, it is necessary to mention angiogenesis and follicular vascularization and their significant role in the aging of the follicles. Receptors for growth factors are present on granulose cells confirming their association with the activation process of the primordial follicles. The most important component in PRP is the transforming growth factor beta family (TGF beta) that plays a significant role during the developmental phases of the follicle (12). A confirmation of all the above statements is also obtained from the Hosseini study (13). This study evaluates the effects of platelet-rich plasma (PRP) on growth and survival of isolated early human follicles in a three-dimensional culture system. The conclusion was that media supplementation with PRP can better support viability and growth of isolated human early preantral follicles in vitro.

On the other hand, the presence of OSCs on the surface of the ovarian tissue, under certain conditions, are able to produce de novo primordial follicles and thus the appearance of new antral follicles. It is noteworthy to mention that only a fraction of the OSCs in culture undergo meiosis to form oocytes. Why only a few cells express Stra8 and undergo differentiation remains unknown (5). Elucidating the mechanisms that cause OSCs to age could lead to new treatments that could delay ovarian aging and slow infertility. In addition, several questions about the mechanism of action of the PRP remain unanswered.

It is clear that several challenges exist when trying to interpret the efficacy of PRP in PORs. There are no standard protocols or standard definitions of poor responders, which can make it challenging to compare studies and perform a meta-analysis (14). Many efforts need to be made before determining the best approach and method for prevention and treatment of PORs.

Limitations, reasons for caution: There are still insufficient controlled clinical trials in the field of ovarian infertility. The limitation of this format should be taken into account i.e. sample size, design, the absence of previous data attesting the safety of PRP injection into ovarian cortex, etc. Future studies are needed to corroborate our results.

CONCLUSION

Because the diagnosis of PORs often leaves limited time for treatment, patients should be given the choice of possible treatments with appropriate information consent. High concentrations of growth factors and cytokines in the PRP in damaged tissue affect the balance between anabolic and catabolic processes, optimizing the tissue environment, and favouring the process of tissue healing.

One-month therapy has the potency of significantly recovering ovarian function both in its hormonal and follicular development abilities. Furthermore, intraovarian injection of autologous PRP in PORs before IVF gives the impression of being a new promising method for achieving better IVF outcome.

Wider implications of the findings: Treatment whit PRP is simple, safe, minimally invasive and with potential cost-effectiveness. In this respect, a continuous interaction between biological and clinical research is vital to develop a proper clinical treatment for a selected group of patients who fulfilled the criteria of poor ovarian responders.

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Disclosure statement

None of the authors report any conflict of interest with this research.

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Original scientific paper

INFLUENCE OF BMI ON RESISTIN IN GDM AND NORMOGLYCEMIC WOMEN

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ABSTRACT

Background: Gestational diabetes melitus is a glucose intolerance which is diagnosed for the first time in pregnancy. It may lead to potentially serious short term and long term maternal, fetal and neonatal complications. In GDM pregnancies biomarkers like resistin are elevated and may provide informations on pathophysiology and prediction of perinatal risk.

Aim: to evaluate the average concentration of resistin in GDM and normoglycemic women,

influence of body mass index on concentration of resistin in GDM and normoglycemic women.

Material and methods: Case control study was made at the University Clinic for obstetrics and gynecology, Skopje in a period of one year. 100 pregnant women were regruted from the pregnant women that performed 75g OGTT in the second trimester for sreening for gestational diabetes melitus. Body mass index was calculated according to the terms of Institute of medicine and pregnant women were divided in 4 groups: GDM BMI>25 (n=25), GDM BMI<25(n=25), normoglycemic BMI>25(n=25), normoglycemic BMI<25(n=25). Serum levels of resistin were analysed with ELISA method.

Results: The average values of resistin in GDM were 3.15 ± 2.02 ng/ml vs 1.94 ± 0.8 ng/ml in the control group, p=0.00021. In GDM, BMI>25 average values of resistin were 3.15 ± 2.0, whereas in GDM, BMI<25 resistin was significantly lower, 1.94 ± 0.8, p=0.0003.

Pregnant women with GDM and BMI>25 had significantly higher average values of resistin (3.16 ± 2.2 ng/ml vs 2.09 ± 0.7 ng/ml, p=0.029) than normoglycemic women with BMI>25. Also pregnant women with GDM, BMI<25 had significantly higher values of resistin than normoglycemic pregnant women with BMI<25 (3.14±1.8 ng/ml vs 1.77± 0.9 ng/ml), p=0.003.

Normoglycemic overweight women had insignificantly higher values of resistin vs normoglycemic women with normal weight (2.09 ± 0.7 ng/ml vs 1.78 ± 0.9 ng/ml; p=0.19).

Conclusion: The results from the study confirmed that GDM significantly alters the values of resistin. In the group of pregnant women with GDM the values of resistin are significantly elevated in women with BMI>25 vs BMI<25. Both women with GDM, BMI>25 and GDM, BMI<25 had significantly higher resistin than normoglycemic women with same BMI. In normoglycemic pregnant women resistin does not have a significant correlation with BMI.

Keywords: resistin, GDM, BMI

INTRODUCTION

Gestational diabetes melitus is a glucose intolerance diagnosed for the first time in pregnancy which may lead to potentially serious short term and long term maternal, fetal and neonatal complications[1].

In GDM pregnancies biomarkers like resistin are elevated and may provide informations on pathophysiology of this condition. Steppan et al in 2001 demonstrated that adipocytes produce unique molecule which is considered as a hormone and called it resistin (which implies for the insulin resistence) [2].

Resistin is a product of the RSTN gene, a peptide hormone from the cistein ritch proteins of the RELM family and is described as a ADSF (adipose tissue specific secretory factor) or FIZZ3 (found in inflammatory zone). The resistin is a polypeptide hormone consisted of 114 amoniacids [3].

It is an adipokine rich wth cysteine and originally described as a molecular bond between obesity and insulin resitence in experimental animals. Because of it's critical role in regulating the insulin sensitivity resistin is implied in the pathogenesis of GDM. Resistin is a hormone produced by monocites, macrophags and adipocites and the placenta [4].

There are 4 physiological roles of resistin: metabolic adaptation of pregnancy, induction of hepatic insulin resistance, regulation of adipogenesis and inflammation.

Romero et al found higher medium level of resistin in pregnancy vs non gravid women. [5]. Resistin concentration in GDM is elevated vs normal glucose tolerance and is connected to proinflammatory interleukin 6 and other markers of insulin resistance [6].

Nicolaides et al investigated the maternal resistin levels in 11-13 g w in normal and pathologigal pregnancies and found that in GDM pregnancies the first trimester resistin levels still are not altered. With progress of the gestational age plasmatic concentration of resistin is increased [7]. Chen, Meggia et al found rapid decrease of resitin levels after birth which suggests contribution of the placenta in resistin production. [8].

The meta analysis of Lobo et al on 10 studies showed that medium concentration of resistin varies between 0.05 and 22.21 ng/ml in the control group and between 0.05 and 62.38 ng/ml in GDM[9]. Cinical studies show a strong correlation between resistin and obesity because serum levels of resistin increase with increase of adiposity [10].

Still consensus has not been reached about the biological role of this newly identified molecule and additional light is needed about the clearing of the pathophysiology of the resistin.

AIM

To establish

-The connection between higher value of resistin and GDM;

-Influence between obesity in pregnancy with GDM on the levels of this biomarker;

- The levels of resistin in normoglycemic women;

-Influence of BMI on levels of resistin in normoglycemic women;

-Informations that would be helpful in clinical practice.

MATERIAL AND METHODS

A case control study was performed at the University Clinic for gynecology and obstetrics in Skopje in the period of 2016 and 2017. One hundred pregnant women which attended the outpatient department for prenatal care at the clinic in that period were included in the study.

Body mass index was calculated by a medical scale (kg/m2) according to the guidelines of Institute of medicine[15]. From the pregnant women that performed 75g oral glucose tolerance test (OGTT) at the biochemical laboratory in the Clinic, women with GDM and normal OGTT were selected at the same gestational age, parity and maternal age. Pregnant women were refered for OGTT from the ob@gyn specialist from primary, secondary or tertiary level of care for performing universal screening for gestational diabetes melitus.

All patients were divided in 4 groups:

Normal OGTT and BMI<25kg/m2 (n=25);

Normal OGTT and BMI>25kg/m2 (n=25);

GDM and BMI <25kg/m2 (n=25) and

GDM and BMI>25kg/m2 (n=25).

Pregnant women were interviewed by a doctor with standard questionare written on Macedonian language.

Criteria for participation in the clinical study:

Inclusion criteria:

-Maternal age 18-45 years;

-Eligibility of the pregnant women for follow up;

-Gestational age confirmed with first trimester ultrasound;

-First prenatal control performed before 20 gw;

-GDM diagnosed with 75g OGTT according to the criteria of the IADPSG [].

Exclusion criteria:

-Pregestational diabetes;

-Chronic hypertension;

-Chronic inflammatory bowel disease treated by corticosteroids;

-Stillbirth;

-Fetal anomalies;

-Amnioinfectious syndrome.

GDM is diagnosed according to the recomendations of the IADPSG [16] between 24 and 28 gw with 75g OGTT (glucose oxydase, Beckman Glucose Analyzer) performed in the morning after night feast with venous blood drawn 60 and 120 minutes after ingestion of 75 g glucose dissolved in 200ml water with cut off values: 0' < 5,1; after 1-h < 10,0; after 2-h < 8,5 mmol/L. Gestational age was calculated by date of last period and confirmed by first trimester ultrasound.

Resistin was analysed from peripheral blood taken from the cubital vein. The serum was obtained by centrifugion (1000xg in the period of 20 minutes) and frozen at -20C for additional analyses after collection of all samples. In a certified laboratory (certificate MKC EN ISO 15189 - 2013) complete analyses were performed: Resistin-completely automated Awareness Technology (USA) – by ELISA method (Enzyme-Linked Immunosorbent Assay). All analyses were performed in the same period and the same time.

Biovendor Human Resistin ELISA is a sandwich immunoassay for quantitative measurement of the human resistin [17]. The standards, the samples and the controls were incubated in a microplate marked with polyclonal anti-human resistin antibodies. After incubation of 60 minutes and washing with biotin, marked polyclonal anti-human resistin antibodies were added and incubated with resistin for 60 minutes. After next washing streptavidin-HRP conjugate was added. After 60 minutes incubation and last washing the rest of the conjugate is responding. Reaction is stoped with adding of acid liquid and absorbence of the rest of the product is measured. The absorbence was proportional to the concentration of the resistin. Standard curve was constructed by plotting value of absorbence vs concentration of standards and concentration of unknown samples determined by using of standard curve.

Limit of detection defined as a concentration of analysis that is giving absorbence higher than the medium absorbence of the blind trial plus three standard deviations calculated by the real values of human resistin is 0.012 ng/ml.

Antibodies that are used in this ELISA test are specific for human resistin with undetectable cross reactivity with human leptin, leptin receptor, RELM-beta on 100ng/ml. Determination of resistin does not interfere with hemoglobin (1.0mg/ml), bilirubin (170mmol/l) and triglicerids (5.0 mmol/l).

STATISTICS

The statistics is made by computer program SPSS 23 for Windows.

-numeric values are given with descriptive statistics (arithmetic median, standard deviation, mediana and interquartal interval);

-qualitative values are shown with apsolute and relative;

-for comparison of analysed groups independent parametric and nonparametric tests (Student t-test for independent samples, Mann-Whitney test);

-for all analyses p value < 0,05 was taken for statistical significance.

RESULTS

Average values of Resistin in GDM vs control group

The average values of resistin in women with GDM were 3.15 ± 2.02 ng/ml vs 1.94 ± 0.8 ng/ml in the control group. In half of the women in the GDM group average values of resistin were above 2.51 ng/ml whereas in the control group values of resistin in half of the women were above 1.87 ng/ml. The results from the study confirmed that GDM significantly alters the values of resistin,

p=0.00021, (table 1).

Table 1- Average value of resistin in GDM vs control group

Group	Descriptive Statistics (Резистин ng/ml)			p value
	mean ± SD	Median	IQR	
GDM	3.15 ± 2.02	2.51	2.06 – 3.12	Z =3.71 p=0.00021 sig
Control group	1.94 ± 0.8	1.87	1.24 – 2.38	

Mann-Whitney U Test

Comparrison of resistin in women with GDM and BMI>25 vs GDM and BMI<25

In the group of pregnant women with GDM the values of resistin significantly depended on the values of body mass index. In the subgroup of overweight pregnant women with GDM average values of resistin were 3.15 ± 2.0, whereas in the subgroup of GDM and normal weight average values of resistin were lower, 1.94 ± 0.8. This difference of 1.21 was statisticaly significant for p=0.0003 (table 2).

Table 2- Average values of resistin in GDM, BMI>25 vs GDM, BMI<25

GDM group				
Групи	Descriptive Statistics (Resistin ng/ml)			p value
	mean ± SD	std err	min – max	
Overweight	3.15 ± 2.0	0.298	1 – 9.55	t =3.78 p=0.0003 sig
Normal weight	1.94 ± 0.8	0.118	1 – 4.15	

t (Student t-test)

Resistin in GDM, BMI>25 vs control group, BMI>25

Pregnant women with GDM and BMI>25 had average values of resistin 3.16 ± 2.2 ng/ml, whereas control group and BMI>25 had values of 2.09 ± 0.7 ng/ml. The difference in average values of 1.07 was statistically confirmed as significant for p=0.029 (table 3).

Table 3- Resistin in GDM, BMI>25 vs control group, BMI>25

GDM (BMI > 25) / control group (BMI > 25)				
Groups	Descriptive Statistics (Резистин ng/ml)			p value
	mean ± SD	std err	min – max	
GDM, BMI>25	3.16 ± 2.2	0.4	1 – 9.55	t =2.26 p=0.029 sig
Control group, BMI>25	2.09 ± 0.7	0.1	1 – 3.59	

t (Student t-test)

Resistin in GDM, BMI<25 vs control group, BMI<25

The pregnant women with GDM, BMI<25 had higher values of resistin than normoglycemic pregnant women with BMI<25 (3.14±1.8 ng/ml vs 1.77± 0.9 ng/ml). The difference between the groups of 1.37 was statisticaly confirmed as significant for p=0.003 (table 4).

Table 4- Average value of resistin in GDM, BMI<25 vs control group, BMI<25

GDM (BMI < 25) CG (BMI < 25)				
Groups	Descriptive Statistics (Resistin ng/ml)			p value
	mean ± SD	std err	min – max	
GDM, BMI<25	3.14 ± 1.8	0.4	1.24 – 8.16	t =3.13 p=0.003 sig
Control group, BMI<25	1.77 ± 0.9	0.9	1 – 4.15	

t (Student t-test)

Resistin in normoglycemic women– BMI > 25 vs normoglycemic and BMI < 25

The pregnant women from the control group which were overweight had insignificantly higher values of resistin vs normal weight women in this group (2.09 ± 0.7 ng/ml vs 1.78 ± 0.9 ng/ml; p=0.19, table 5).

Resistin in normoglycemic women, BMI > 25 vs normoglycemic women, BMI < 25

Control group				
Groups	Descriptive Statistics (Resistin ng/ml)			p value
	mean ± SD	std err	min – max	
Overweight	2.09 ± 0.7	0.1	1 – 3.59	t =1.34 p=0.19 ns
Normal weight	1.78 ± 0.9	0.12	1 – 4.15	

t (Student t-test)

DISCUSSION

Biomarkers are any body supstances than can be quantified and represent normal body physiology, patogenetic mechanism or pharmacological response to treatment.

Biomarkers can be either markers for risk for a disease or screening tool for identification of a disease in a subclinical phase ().

Many studies confirmed that higher values of resistin and IL-6 in GDM can say about the role of low grade inflammation in the pathogenesis of this disease. Meta

analyses of 10 studies from Lobo et al about medium concentration of resistin in pregnancy less and more than 32 gestational weeks in normoglycemic women showed variation between 0.05–22.21 ng/ml and in GDM between 0.05–62.38 ng/ml [10]. In our study average values of resistin were between 3.15 ± 2.02 ng/ml vs 1.94 ± 0.8 ng/ml in normoglycemic women and we have proved that resistin in GDM is significantly higher than in normoglycemic women (p=0.00021). This is similar to findings of Kuzmicki et al [6].

Increased maternal weight in pregnancy has a rising prevalence worldwide and represent a major obstetric problem increasing the maternal and neonatal morbidity and mortality.

Wishing to establish the influence of body mass index on this biomarker we compared the value of resistin in pregnant women with GDM: overweight and women with normal BMI.

In women with GDM and BMI>25 average values of resistin were 3.15ng/ml and significantly higher than GDM and BMI<25, 1.94 ng/ml (p=0.0003).

The same comparison was made in normoglycemic pregnant women and established that BMI did not have a significant influence on values of resistin (2.09 ± 0.7 ng/ml in BMI>25 vs 1.78 ± 0.9 ng/ml in BMI<25, p=0.19).

Comparison was made between overweight pregnant women with or without GDM and resistin was significantly higher (3.16ng/ml vs 2.09ng/ml, p=0.029).

In pregnant women with normal weight with or without GDM resistin was significantly higher in GDM women (3.14ng/ml vs 1.77ng/ml, p=0.003).

CONCLUSION

Out study showed that resistin, a marker for insulin resistance is significantly elevated in GDM compared to pregnant women with negative OGTT. In pregnant women with GDM resistin was significantly higher in overweight vs normal weight women. Pregnant women with GDM both overweight and normal weight had significantly higher resistin than normoglycemic pregnant women with same BMI. In normoglycemic pregnant women resistin was elevated in overweight vs normal weight women but not enough for statistical significance.

Further studies are needed for evaluation of the clinical aspect of resistin in GDM pregnancies and it's connection to BMI in normal weight and overweight pregnant women.

Keywords: resistin, BMI, gestational diabetes melitus

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Original scientific paper

CORRELATION BETWEEN IL-6 (INTERLEUKIN 6) AND LABORATORY PARAMETERS (CRP, TOTAL PROTEINS AND LDH) FOR VERIFICATION OF THE INFLAMMATORY ORIGIN IN PREECLAMPSIA

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ABSTRACT

In normal pregnancy there is a transfer to the Th2 anti-inflammatory type of immunity, directed toward the fetus and the placenta, whereas in pregnancy complications, such as preeclampsia due to absent transfer, Th1 or proinflammatory immune system is dominated. This article analyzes what are the most important circulating biomarkers created by syncytiotrophoblast that together combined and promote oxidative stress. An increase in proinflammatory and decline in the antiinflammatory cytokine is an imbalance that explains the theory that due to impairement of the immunological response, consequences on the mother's circulation are developed and are reflected in the manifestation of pregnancy complications such as preeclampsia and intrauterine growth restriction.

The purpose of the study is to emphasize the importance of the results of the correlation between interleukin 6, measured in the serum of patients from 14 to 20 gestational weeks, with laboratory parameters that are pathognomonic for preeclampsia (LDH, total protein and CRP). This explains the immunological and inflammatory response in preeclampsia serving as a predictor of the condition.

For that purpose, the materials and methods that were used were 100 patients examined at the University Clinic of Obstetrics and Gynecology, divided in two groups. The first or examined group consists of 50 patients with notch of the uterine artery present in the second trimester from 14 to 20 gestational weeks. The second, or control group consists of 50 patients with absent notch of the uterine artery. These patients are then referred to the Institute of Immunobiology and Human Genetics at the Faculty of Medicine in Skopje to examine the levels of cytokines, in particular the relationship between the proinflamatory with antiinflammatory cytokines (TNF-α, IL-6 vs. IL-10) using ELISA (enzyme-linked immunosorbent assay) methodology, with Magnetic Luminex Assay multiplex kit.

The results between the examined and the controlled group verified an increase in proinflammatory (TNF-α and IL-6) and a decrease in the antiinflamatory cytokine (IL-10), from which the variance of the level IL-6 showed important statistical significance $p<0.01$. Positive correlation was of great statistical significance between levels of cytokine IL-6 and increased levels of LDH and CRP, and with decreased levels of the total proteins of the preeclamptic patients. (LDH $p<0.00001$, CRP $p<0.025$ and total proteins $p<0.0012$).

The role of the inflammatory response is obtained by the correlation of the interleukins in the second trimester and laboratory examinations in the third trimester as a sufficient predictive method in detection in early stages the preeclampsia syndrome.

Keywords: Preeclampsia; prediction; interleukins, predictive metod.

INTRODUCTION

Preeclampsia is a hypertensive disorder in pregnancy, followed by proteinuria, after the 20th gestational week with multifactorial etiology. The etiopathogenesis includes genetic, immunological, hematological, angiogenic theory, induced oxidative stress, maternal endothelial dysfunction and inappropriate remodelling of the spiral arteries. These contributes to the development of ischemia and hypoxia which subsequently induce promotion of bioactive substances and immunological biomarkers.

There is a complex relationship persisting between immunology, inflammation and preeclampsia. That connection is presented in pregnancy through adaptation of the immunological response needed for the mother to tolerate the different immunological system of the fetus throughout the entire pregnancy. Laura A. Mageea et al. (2014) stated that preeclampsia can be result of an inflammatory cause [1].

In the process of trophoblast invasion, the decidua, which forms the mother's side of the placenta, contains a large number of immune cells necessary for proper migration of trophoblast cells. Macrophages, NK (natural killer) cells, DC (dendritic cells), T regulatory cells are present in the decidua and are required for normal invasion of the trophoblast cell for placentation [2, 3].

These cells jointly infiltrate the decidua and together with the trophoblast cells make a conglomerate allowing it to reach the endometrium through controlled removal of the spiral artery's native cells. Uterine NK cells, T regulatory cells and regulatory cytokines provide adequate control and function of proinflammatory cells in their activity to ensure proper invasion. Namely, DC cells from the decidua through their function promote Th2 cells to make the mother immunotolerant to the fetus. In summary, immune cells in pregnancy produced by the decidua have the role of providing proper implantation and promoting trophoblast invasion, which is neither superficial nor overly invasive. This is achieved by the production of cytokines and angiogenic factors, which are necessary for normal pregnancy [4].

Damage to this process, especially in the myometrial part of the blood vessels, is predisposed to complications such as preeclampsia, intrauterine growth restriction, preterm birth or fetal death [5]. It is manifested with increased resistance in the blood flow and appearance of notch of the uterine artery.

In order to properly invade the walls of the myometrium, the distal column cytotrophoblast expresses a number of extravilial trophoblast markers such as HLA-G, T cell factor 4 (TCF-4), integrin ɜ5 (ITGɜ5) and ɜ1, Notch2, proteoglycan 2 and ErbB2 [6].

Taking a genetic overview, TNFSF13B is a member of tumours necrosis factor ligands. It is located on chromosomal region 13q32-q34 and is responsible for regulating the immunological response to infections, autoimmune diseases and inflammation. It is assumed that it modulates the mother's immunological tolerance to the fetus.

TLRs (toll-like receptors) are involved in host defence against external microbes. They are central components of the humoral immune system. The allelic variants of the humoral immune system TLR-4 (toll-like receptor-4) and the NOD2 gene (apoptosis regulator) are correlated with high IL-6 values in patients with early onset preeclampsia. They also have immunosuppression of the T regulatory cells [7].

TNF-α (tumour necrosis factor α) stimulates the production of angiotensin II in the female reproductive system, while in combination with IL-6, it participates in increased production or expression of angiotensin II type 1 receptors in the smooth muscle of blood vessels [8].

IL-6 (interleukin 6) is an equally important proinflammatory cytokine, produced by mononuclear phagocytes, endothelial cells, fibroblasts, and T cells and is involved in immunological activation, i.e., the function of the vascularisation in the modulation of the immunological response. The imbalance caused by the increase in proinflammatory and decline in the antiinflammatory cytokine explains the theory that due to impairment of the immunological response develops overall consequences on the mother's circulation which are reflected in the manifestation of pregnancy complications such as preeclampsia and intrauterine growth restriction.

In preeclampsia, due to placental ischemia and consequently present endothelial dysfunction, the balance of their proper synthesis and function is disturbed. Increased levels of the proinflammatory cytokines correlate with endothelial cell permeability, manifested by increased blood preassure and decreased renal function (pathologically renal tissue is glomerulosclerotic, glomeruli show harneded outlook with major constriction or occlusion). The capillary

endothelium is edematous with thickening of the capillary basal membrane and enlargement of interstitial spaces with intense edema as proven by Sien Yee Lau et al. [9].

PURPOSE

There is a correlation between the increased value of interleukin 6, proinflammatory cytokine, measured in the serum of patients from 14 to 20 gestational weeks, and laboratory parameters that are divergent and are pathognomonic for preeclampsia (LDH, total protein and CRP). The purpose of this study is how reflects the immunological and inflammatory response in preeclampsia serving as a predictor and signal for her preventive treatment.

MATERIALS AND METHODS

The study is a prospective cohort, comprising of 100 patients examined at the University Clinic of Obstetrics and Gynecology, who have previously written informed consent to participate in the study. They are divided into two groups:

The first or examined group consists of 50 patients with notch of the uterine artery present in the second trimester from 14 to 20 gestational weeks as the main inclusion criterion. The second, or control group consists of 50 patients with absent notch of the uterine artery. The inclusion criteria are the presence of a notch of the uterine artery, and the exclusion criteria are twin pregnancies, chromosomal abnormalities, and dead fetuses.

These patients are then referred to the Institute of Immunobiology and Human Genetics at the Faculty of Medicine in Skopje, for analysis of circulating immune biomarkers in the patient's serum, i.e. to examine the levels of cytokines, in particular the relationship between the proinflamatory with antiinflammatory cytokines (TNF-α, IL-6 vs. IL-10). They are developed by ELISA (enzyme-linked immunosorbent assay) methodology, using the Magnetic Luminex Assay multiplex kit (figure 1).

The results were subjected to statistical analysis and processing with computer programs: STATISTICA 12 and SPSS 21.0 for Windows. On this basis, tests for significance of differences between the comparison groups of all the parameters analyzed were performed.

Patients are monitored further in the third trimester if they will develop clinical symptomatology for preeclampsia verified by basic diagnostic criteria, and laboratory deviations are compared and set in correlation with the results of the cytokines obtained.

With the correlation, the idea is to see how deviations in the second trimester in the ratio of the interleukin values can be a predictive parameter for the development of preeclampsia.

Figure 1: Kit used for development of interleukins

RESULTS

The results of the two investigated groups, examined (48) and control (48) patients, and were processed. Four patients (2 from the examined group and 2 from the control group) left the study for medical malcondition and pregnancy loss.

Anamnestic data such as age, positive family history, parity, BMI, pre-comorbidities, preeclampsia in previous pregnancy were analyzed and a statistical significance was found only in relation to the anamnestic data of previous pregnancy with preeclampsia ($p < 0.05$). Comparison of the other parameters showed no statistically significant result.

Using the ELISA methodology, values of cytokines (TNF-α IL-6 versus IL-10) were obtained from both the control and the examined group to obtain appropriate conclusions.

Table 1: Analysis of interleukins between the examined and control groups (standard deviation and standard mean error)

Group of patients	Number	Mean Value	Std. Deviation	Std. Error Mean
Examined (TNF-α)	48	4.4965	1.42655	0.21266
Control (TNF-α)	48	4.2547	0.98405	0.13779
Examined (IL-6)	48	3.2177	4.00221	0.59661
Control (IL-6)	48	0.7166	.53494	0.07491
Examined (IL-10)	48	1.3943	3.49554	0.52108
Control (IL-10)	48	6.1853	40.28594	5.64116

TNF-α in patients in the examined group, i.e. those with verified notch on the uterine artery, ranged from the lowest 1.59 to the highest 8.29 pg/ml with a mean of 4.49 and SD of 1.42 which is 5% higher value than the control group.

Then, IL-6 in the patients of the examined group variates in span from 0.64 at the lowest to 15.25 pg/ml, as the highest with a mean value of 3.2 pg/ml and SD of 4.0 which is three times higher value than the control group.

The IL-10 in the examined group is presented with a mean value of 1.39 pg/ml with SD 3.49, ranging from 0.54 to 20.70 pg/ml which in comparison with the control group has a tendency of a sharp decrease with five times lower value.

Using the T-test for significance of the differences between the two comparison groups (with and without notch), the following table shows that the only statistically significant result is in the value of IL-6, ($t = 4.422$, $p < 0.01$), where it is evident that patients who have notch from the examined group have higher IL-6 values than patients from the control group.

No statistically significant differences were observed among the other parameters ($p > 0.05$).

Table 2: P-test for significance and T-test for significance of differences between test and control group

	T-test for significance of differences						
	t	Df	P-test (Significa t -(2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
						Lower	Upper
TNF-α	0.976	94	0.332(NS)	0.24182	0.24777	-0.25014	0.73379
	0.954	76.792	0.343(NS)	0.24182	0.25340	-0.26278	0.74643
IL-6	4.422	94	0.000*	20.50116	0.56568	1.37799	3.62433
	4.160	45.388	0.000*	2.50116	0.60130	1.29037	3.71195
Il-10	-0.795	94	0.429(NS)	-4.79099	6.02910	-16.76192	7.17994
	-0.846	50.853	0.402(NS)	-4.79099	5.66518	-16.16510	6.58312

Statistical analysis using multivariate regression analysis of the three obtained statistical procedures revealed that, of all the interleukins that differ, IL-6 had the highest statistical significance at $p < 0.01$.

Table 3: Statistical analysis, coefficients of multivariate logistic regression analysis of interleukins in preeclampsia

Model		Unstandardized Coefficients		Standardized Coefficients	T	P significance
		B	Std. Error	Beta		
1	(Constant)	1.817	0.360		5.044	0.000
	TNF- α	0.008	0.041	0.020	0.197	0.8449(NS)
	IL-6	-0.072	0.016	-0.432	-4.351	0.000*
	IL-10	0.002	0.002	0.122	1.279	0.204(NS)

*The result is significant at $p<0.05$

(NS) The result is not significant at $p>0.05$

Dependent variable: patients with preeclampsia

Based on the above, the patients were examined in the third trimester, of which preeclampsia was developed after 31 gestational weeks. Of the 48 patients, 32 had abnormalities and interleukin imbalances, and 21 developed clinical preeclampsia syndrome. The other 11 patients had other comorbidities and a false positive result.

Regarding systolic, diastolic blood pressure, lactate dehydrogenase, C-reactive protein, total proteins, proteinuria and 24-hour proteinuria, there was a statistically significant result in the $p < 0.05$ groups studied.

Correlation between IL-6 as the most significant predictive parameter of the statistical multivariate regression analysis and some of the deviations in laboratory parameters in addition to preeclampsia were made that resulted in statistical significance.

The aim is to establish the fact that previously raised values of proinflammatory interleukins in the serum in the second trimester correspond to the values of laboratory parameters that are stigmatized for advanced preeclampsia in the third trimester.

Table 4: Correlation between IL-6 with LDH, CRP, and Total Proteins

Correlation		LDH	CRP	Total proteins
IL-6	Pirsons coeficient of corrrelation	0.9108	0.486	-0.6563
	P – significance	<0.00001*	0.025501*	0.001242*
	Number of patients with PE	21	21	21

*The result is significant at p<0.05

From the results shown in Table 4. where the Pearson coefficient of correlation between the variables is used, it can be concluded that in preeclampsia patients with increasing IL-6 value and growth of the LDH value (0.91) show a statistically significant result with p <0.001, i.e. there is a positive correlation between them.

The same is obtained by the correlation between the increase in IL-6 values and the increase in CRP values, which is an explanation that the etiology of preeclampsia is dependent on the patient's immune response (0.48 i.e. p <0.025).

Conversely, showing a correlation between increased IL-6 and decreased total protein results, which is in favour of hypoproteinemia in preeclampsia, which is also a statistically significant result (p <0.0012).

The course of pregnancies and birth has been followed, i.e. how many patients have developed maternal and fetal complications according to the urgency and measures taken for a better perinatal outcome. That is a subject of other study.

DISCUSSION

Immunological modulators represent a direct complement for early detection of preeclampsia. Its symptoms of hypertension, proteinuria, deviations in laboratory parameters in addition to an increase in degradation products, and a decrease in protein derivates in the blood and the presence of proteinuria have been diagnosed. Subsequently rich symptomatologies from sight disorder, edema to fulminant endangerment of the mother's condition or endangerment of the fetus have been diagnosed. Many authors and colleagues appreciate professor Redman as one of the founders of the understanding of the etiology, pathology, diagnosis, and management of preeclampsia. The importance of the immunological system and the presence of immune factors Redman analyzes in detail [10].

According to him, the inflammatory response is induced by placental particles, ranging from large deposited multinuclear fragments to subcellular fragments distributed along the surface of the human placenta. Changes in the number and magnitude of syncytrophobic exosomes and blood vessel damage with microdimensions are very important in maternal preeclampsia syndrome. Yanfang Guo et al. through numerous studies elaborate the immunological base as a trigger factor in the maternal systemic circulation [11]. Walker JJ writes on the same topic, stating that it is a failure or deficiency in the normal defence mechanism to the fetus. Interleukins such as IL-6, IL-8, and TNF-ɜ grow at the same time with lipid peroxidase, proving their monocyte origin [11]. Stimulated monocytes produce free radicals that cause oxidative damage. Maternal cells are protected from plasma and intracellular oxidants. The very imbalance between oxidants and antioxidants and subsequent change in membrane oxidation leads to instability of membrane permeability which is the basis of clinical manifestations of preeclampsia. Genetic modification and change in differentiation in the production of TNF-ɜ and nitric oxide, also modifies the development of the disease [12].

In our study, proinflammatory interleukin TNF-ɜ is increased, as well as nitric oxide and by Pearson correlation between the variables it is verified that not only does it grow, but it grows at the same time with IL-6, p = 0.017 which is a statistically significant result.

The results of this study were compared with those of Teran et al., [13] and Hentschke et al., [14] who also analyzed the increase in plasma cytokine levels and verified an increase in IL-6 in preeclampsia. Afshar et al, [15] found an increase in IL-6 but not a common increase in TNF-ɜ while Olusi et al. [16] found at the same time a symmetrical increase in both IL-6 and TNF-ɜ and in some of the normal pregnancies. The comparison in these investigations is significant to be performed at the same time. It is of very importance the impact of gestational age, the multiparity, the amount of blood derivates sample taken, because of the differences in the dilutions and the kits with which the interleukins themselves are

pronounced and by which methodologies and whether patients are undergoing some therapy.

In the study by Ifeoma Udenze [17], he reported a statistically significant result in the levels of proinflammatory cytokines, IL-6 and TNF-ɜ and in CRP levels in women with severe preeclampsia compared with women with normotensive pregnancy. The high levels of IL-6 and TNF-ɜ found in association with CRP values in severe preeclampsia have a significant clinical contribution to the theory that preeclampsia is indeed due to exacerbation of the inflammatory response. His analyzes are consistent with those of Cui Xie et al., in order to confirm the above theory [18]. The results of this study correspond to the results of Udense because a correlation was made and a statistically significant correlation was found between IL-6 as most significant with CRP with $p < 0.05$ $p = 0.025$ which is in favour of impaired immune response. A correlation of IL-6 with LDH and total protein was also performed, which also resulted in a statistically significant result corresponding to $p < 0.01$ and is a risk signal for the development of organic affection and the development of hypoproteinemia with proteinuria in addition to the development of preeclampsic symptoms. The present imbalance in the immune response, i.e., higher values of proinflammatory parameters are reflected as follows. High levels of IL-6 and TNF-ɜ systemically induce the inflammatory response through the hepatal cells to stimulate the synthesis of CRP, or C reactive protein, which is a sensitive marker for tissue damage and inflammation of tissues, which is an indication of the rate of inflammation, oxidative stress and their correlation with preeclampsia.

CONCLUSION

From the results obtained and the discussions, it can be seen that with correlation of the interleukins in the second trimester and laboratory examinations in the third trimester, insight into patients at increased risk for development of clinical preeclampsia syndrome can be provided. It was confirmed and in our investigation. This enables careful follow-up of these patients for the purpose for prevention, prediction, diagnosis and appropriate early treatment of preeclampsia.

The whole point is through investigation of the correlation between the interleukins and laboratory parameters for verification of the inflammatory origin in preeclampsia to have a better perinatal outcome and well-being for both the mother and the fetus.

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Original scientific paper

ENDOSCOPIC FINDINGS IN THE STOMACH AS A RESULT OF TREATMENT WITH NSAID

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ABSTRACT

The digestive system can often be attacked by excessive and irregular use of NSAID drugs. There is a so-called mucosal barrier that plays a major protective role against aggressive agents. If any of the protective components is damaged, the mucosal barrier becomes flaky, equilibrium breaks down thus causing destruction of mucosal cells, consequently, disorders of different types, from those with microscopic, millimeter dimensions to large, macroscopic changes that can cause bleeding and end to fatality. The main objectives of this study were to investigate endoscopic findings in the stomach as a result of the use of these drugs.From endoscopic findings, most common were chronic gastritis, erosive chronic gastritis and gastric ulcer.The duration of taking these drugs is in the right proportion with their side effects in the stomach. The side effects of NSAID in the stomach are more frequent at the older ages. The most vulnerable age group is over 65. NSAID of the selective COX-2 group have priority over the non-selective COX-group. Giving NSAID should be associated with gastric protectors such as H2-receptor inhibitors and proton pump inhibitors especially in high-risk patients with gastric problems.

The key words: NSAIDs, stomach, COX non selective, COX selective

INTRODUCTION

The digestiv system can often be challenge by excessive and non-regular use of non-steroidal anti-inflammatory drugs (NSAID). There is a so-called mucosal barrier that plays a major protective role against aggressive agents.[1]

If any of the protective components is damaged, the mucosal barrier becomes flaky,equilibrium breaks down by initiating mucosal cell destruction, with consequence, disorders of different types, from those with microscopic dimensions, milimetrics, to big changes, macroscopic, which can cause bleeding and that can end with fatality. This can occur or by damaging or reducing the protective factors that make up the mucosal protective barrier,or by adding aggressive factors such as gastric acid to some pathological conditions.[2,3]

There are a number of factors that may lead to this imbalance, among them is the excessive and uncontrolled use of NSAD. Irritation of the gastrointestinal tract from these drugs can be initiated by two ways, in direct or indirect way. As acid molecules, these drugs directly irritate the gastric mucosa, and in indirectly way, systemic,by inhibiting the cyclooxygenase enzymatic system (COX-1 and COX-2), reduce the level of protective prostaglandins in the blood. Inhibition of prostaglandin synthesis in the digestive tract causes increased secretion of gastric acid, reduction of the secretion of bicarbonates, reduction of mucus secretion and consequently, reduction of trophic effect in epithelial mucous membranes.[4,5] Gastric acid plays a central role in mucosal injuries associated with the use of NSAID.[6,7] Peptic ulcers caused by the use of NSAID are related to the systemic effect of these drugs. Such a mucosal injury occurs regardless of the way in which they are administered(oral, rectal, or parenteral) and may also appear in patients with aclorhidry.[8]

Risk of ulcer manifestation,increases with the increase in the duration of use as well as with the addition of NSAID doses.[9]

PURPOSE OF PROJECT

The purpose of this paper was that, by the endoscopic method,analyze the changes in the stomach,caused as a result of the use of NSAID in correlation with the age of the patients and the duration of the drug intakealways comparing the group that used non-selective NSAID to selective (Cox-2).

MATERIAL AND METHODS

The work was performed at the Clinic of Rheumatology and the Endoscopic Cabinet of UCCK Gastroenterology Clinic in Prishtina.Are examinated a total of 156 patients with rheumatic problems were treated with NSAD. from them,111 who were treated with non-selective group NSAD (Diclofen, Brufen dhe Ketonal), while 45 with selective group drugs (Meloxicam and Celecoxib). All patients have been realized the gastroscopy to see and analyze changes in the stomach.

RESULTS

After appropriate endoscopic examinations and their statistical processing, we have achieved the following results:

Table 1. Researched by groups and gender

Gender	Gr.1 (Non selective)		Gr.2 (Selective)		Total	
	N	%	N	%	N	%
F	57	51.4	20	44.4	77	49.4
M	54	48.6	25	55.6	79	50.6
Total	111	100.0	45	100.0	156	100.0
X2-test, P-value	X2=0.366, P=0.545					

In the study are involved 156 patients divided into two groups; in group 1 who used standard non-selective drugsand group 2 that used standard selective drugs. In Gr.1 are involved 111 patients (or 71.2%) and Gr.2 involved 45 patients(or 28.8%).Of the total number of patients 77 or 49.4% were female and 79 or 50.6% male.

Table 2. Endoscopy results by groups

Endoscopy results	Gr.1 (non selective)		Gr.2 (Selective)		total	
	N	%	N	%	N	%
Chronic gastritis	44	39.6	35	77.8	79	50.6
Chr. Gastritis erosiva	23	20.7	7	15.6	30	19.2
Gastritis ulcera	44	39.6	3	6.7	47	30.1
Total	111	100.0	45	100.0	156	100.0
X2-test, P-value	X2=21.2, P<0.001					

Table 3. Age Parameters according to Endoscopy Results and Groups

Age (Year) Chronic gastritis		Endoscopic results		
		Chr. Gastritis erosiva	Gastritis ulcera	
Gr. 1	N	44	23	44
	Average	49.9	57.9	61.9
	DS	12.8	14.1	13.2
Gr. 2	N	35	7	3
	Average	51.1	56.7	77.0
	DS	14.7	13.9	2.6
T-test, P-value		T=0.387 P>0.05	T=0.290 P>0.05	T=1.95 P>0.05

Table 4. Duration of treatment according to endoscopy results and groups

Treatment time (Year) Chronic gastritis		Endoscopic results		
		Chr. Gastritis erosiva	Gastritis ulcera	
Gr. 1	N	44	23	44
	Average	2.9	5.2	6.2
	DS	2.2	2.4	2.7
Gr. 2	N	35	7	3
	Average	5.7	6.3	10.3
	DS	2.2	2.9	0.6
T-test, P-value		T=5.61 P<0.001	T=1.40 P>0.05	T=2.60 P<0.05

Table 5. Types of gastric ulcer by groups

Ulcera	Gr.1 (non selective)		Gr.2 (Selective)	
	N	%	N	%
Forrest Ia	2	4.5	-	-
Forrest Ib	1	2.3	-	-
Forrest IIa	4	9.1	-	-
Forrest IIb	4	9.1	-	-
Forrest IIb/c	2	4.5	-	-
Forrest IIc	2	4.5	-	-
Forrest III	9	20.5	-	-
Pa specifikuar	20	45.5	3	100.0
Total	44	100.0	3	100.0

Of the 44 cases with Gastric Ulcer of Group 1, 20.5% were Forrest III, 27.2% Forrest II, 6.8% Forrest I while 20 cases or 45.5% were not specified. In group 2 we had 3 cases with gastric ulcer and all three were unspecified (Table 5).

DISCUSSION

NSAIDs cause side effects in many organs of the human body and among these effects,the most common ones are those in the digestive tract.Prevalence of gastric ulcer in patients who regularly use NSAID drug is about 15-30% while the annual incidence of complications in the upper abdominal tract of the AIJS users is approximately 2.5-4.5%.[10] Changes in the digestive tract due to the use of these drugs are of the most varied, ranging from the smaller and insignificant ones to the gastric mucosa, to those of a size that could endanger the patient's life.In some cases, Gastrointestinal symptoms caused by NSAID can be quite severewith a risk of 6 to 7 times greater to be caused compared to the use of other drugs.[11]

Using NSAID COX2-selective can be very useful in patients who are treated for a long time with NSAID as well as those who are at high risk of becoming sick with peptic ulcerative disease.[12]

In many studies done, it has been found that the use of selective NSAID such as Celecoxib, significantly reduce the risk of causing gastric ulcer compared to non-selective NSAID such as Naproxen and Diclofenac.[13,14]

In our case, abnormal changes have been found in all patientsin gastric mucous membranes described with endoscopy such as Chronic Gastritis, Erosive Chronic Gastritis and Ulcer Gastric. While gastric ulcers in Group 1 have been found in 44 cases or 39.6%, in group 2 it is only described in 3 or 6.7% of caseswhich is consistent with literature and studies by other authors on the added affinity of non-selective NSAIDsto cause Ulcerative Peptic Disease compared to the selective group.

According to a study done at Maryland University in 2011, it has been found that a large number of factors cause Chronic Gastritis including long periods of NSAID use, added acidity in the stomach as well the ages of the patients who use these herbs.[15] In our study is concluded as well something like that.Although the average duration of treatment in group 1 was shorter compared with group 2 (4.7 year : 6.1 year), still gastric barriers remain were most expressed in group 1.

It is very important to note that the bleeding from the stomach, the obstacle that has been found only in patients treated with non-selective NSAIDs, the median duration of treatment was the highest with 7.29 yearswhich speaks of a fair correlation between the long-term treatment and their side effects.

Gastric changes like Chronic Gastritis, Erosive Chronic Gastritis and Peptic Ulcers, are found in the largest number of patients who have been treated for a long time with these drugswhile those who have been treated for a short period of time,they are found in smaller numbers. In

Group 1 cases with Peptic Ulcer, the median of treatment was the highest with 6.2 years compared to the median of Chronic Gastritis and Erosive Chronic Gastritis which proves the duration of treatment as a risk factor for the appearance of abnormal changes in gastric mucosa.

If we compare the patients of the first group to the second group, we can say that, despite the longer treatment time for Group 2 patients, there is still a significant difference in the presentation of these changesas they are found in the highest percentage of patients in the first group. While in the first group, 44 cases with Peptic Ulcer were identified, 20 of which with signs of bleeding (grouped at Forrest of various degrees), in the second group only 3 cases of peptic ulcers were recorded, which did not bleed.

Side effects of NSAID are related to the age of the patients using these drugs. The greater the age, the more frequent are the side effects in the digestive tract.[16]

In a study by Sommerville with partners, Peptic ulcers were found at least twice as many in the elderly over 65 who used NSAID compared to those who did not use these drugs and compared to the youngest age groups. The risk for the appearance of bleeding peptic ulcer is increased significantly to users of these drugs in this age group.[17]

Even in our results, the age group that most resulted with gastric disabilities was over 65 years.

By analyzing endoscopic findings in group 1, we found a dominance of gastric changes at the older ages.Peptic ulcers as a more heavily complication compared to other gastric changes, was found at the highest average age (61.9 years) compared to CG (49.8 years) and ECG (57.9 years).

Also in group 2, Peptic ulcer is found at old ages, so the average age is 77 years compared to other findings that are noted at younger ages.

vehte If we compare the groups between themselves, it is seen that Peptic Ulcer in group 1 is presented at an average age of 61.9 years compared with group 2 where this pathology has appeared in the average age of 77, which also marks a priority of COX-2 selective drugs versus COX non selective.

CONCLUSION

After analyzing and processing the results obtained from this research, compared with data from literature and many other relevant studies, we ascertain that:

NSAID cause a variety of changes in the gastric mucous membrane.

The duration of taking these drugs is in the right proportion with their side effects in the stomach, therefore the longer the treatment time is, the greater will be the harmful effects.

The side effects of NSAID in the stomach are more frequent at the older ages and the most vulnerable age group is over 65.

NSAID of the selective COX-2 group have priority over the non-selective COX-group especially in high-risk groups to develop digestive problems such as older ages and patients with long-term care.

Giving NSAID should be associated with gastric protectors such as H2-receptor inhibitorsand proton pump inhibitorsespecially in high-risk patients such as older ages, patients with chronic illnesses needing long-term treatment as well as patients with positive history of gastroduodenal problems.

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Original scientific paper

,КОРЕЛАЦИЈА ПОМЕЃУ ДЕРМОСКОПСКИТЕ ТИПОВИ НА АКВИРИРАНИ НЕВУСИ И ВОЗРАСТА

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АПСТРАКТ

Дермоскопија(син.епилуминисцентна микроскопија, површна микроскопија, дерматоскопија) претставува ин виво, не инвазивна метода за опсервација и дијагноза на пигментните кожни лезии. Терминот дермоскопија кој е најшироко прифатен , за прв пат сугериран од Fridman et al.

Дермоскопијата користи оптичко зголемување лупа и халогена светлина и по потреба течен медиум за минимизирање на рефлексијата.

Со дермоскоп може да се визуелизираат структури кој не се видливи со голо око.Тоа се структури кои се наоѓаат во епидермис, дермо-епидермалната јункција,папиларниот и дел од ретикуларниот дерм.

Меланоцитните невуси (МН) се бенигни неоплазми .Клинички се презентираат како јасно ограничени пигментни лезии,хистолошки се состојат од невусни клетки.

Тие се класифицираат на конгенитални и аквирирани,предмет на ова истражување се аквирираните невуси. Поделени спрема морфологијата на пет типа(глобуларни, ретикуларни, мешани со пигментна мрежа на периферијата, мешани со глобули во периферијата и неспецифични.

Цели на студијата е утврдување дали постои корелација помеѓу различните демоскопски типови на невуси во зависност од возраста.

Студиите кој ги проучуваат дермоскопските типовите на невуси можат да дадат допринос во изработка на попрецизни дијагностички алгоритми како и предктивни модели за попорецизна дијагноза во однос на пигментите тумори.

ВОВЕД

Дермоскопија(син.епилуминисцентна микроскопија, површна микроскопија, дерматоскопија) претставува ин виво, не инвазивна метода за опсервација и дијагноза на пигментните кожни лезии.1 Терминот дермоскопија кој е најшироко прифатен , за прв пат сугериран од Fridman et al.2

Дермоскопијата користи оптичко зголемување лупа и халогена светлина и по потреба течен медиум за минимизирање на рефлексијата.

Со дермоскоп може да се визуелизираат структури кој не се видливи со голо око.Тоа се структури кои се наоѓаат во епидермис, дермо-епидермалната јункција,папиларниот и дел од ретикуларниот дерм.

Оваа метода има голем бенефит во диференцијација на немеланоцитни од меланоцитни лезии,диференцирање помеѓу бенигни и малигни лезии,сензитивноста во дијагностика на меланомот е 90% наспрема 74% клиничка дијагноза.Исто така со нејзина помош се избегнува бројот на непотребните ексцизии и овозможува следење на пациенти со мултипли невуси.3

Техниката на изведување на дермоскопијата е

мошне едноставна,брза и ефтина.Таа е не инвазивна метода,се изведува ин виво ,така што самиот апарат се приклонува на лезијата која треба да се гледа.Може да се користи течен медиум (гел,масло,алкохол) кој го подобрува контактот на дермоскопот со лезијата и при тоа ја намалува рефлексијата.

Ова техника се однесува на едноставната дермоскопија,за траен запис и фотодокументација се користи дигитална и видеодермоскопијата

Невуси

Меланоцитните невуси (МН) се бенигни неоплазми .Клинички се презентираат како јасно ограничени пигментни лезии,хистолошки се состојат од невусни клетки.

Невусните клетки водат потекло од неуралната криста(срт) и мигрираат во текот на ембриогенезата примарно во кожата,ЦНС,очите и ушите.4

Невусните клетки А (епителоид) еволуираат во клетки Б (лимфоцитоид) и потоа во клетки Ц (неуроид).Следните морфолошки карактеристики ги одвојуваат невусните клетки од меланоцитите(немаат дендрити,аранжманот им е во гнезда ,поголеми се од меланоцитите,поголема цитоплазма и содржат гранули локализирани во епидермисили дермис ретко во субкутис.)

Невусните клетки го претставуваат финалниот стадиум на еволуција од неуралната криста прекурсорна клетка во невобласт.Од друга страна има тврдења дека невоцитите и меланоцитите настануваат од иста прекурсорна клетка -меланобласт.

Меланоцитните невуси спрема потеклото се класифицирани во ;

I.Конгенитални невуси

II.Аквирирани невуси

-Типични аквирирани невуси

-Атипични (диспластични) невуси

-Плав невус

-Хало невус

-Спитц невус

Аквирираните невуси (АН) се мали најчесто помали од 1 см,добро ограничени,пигментирани кои се состојат од невусни клетки.Во однос на бојата се во нијанси на кафено и граници кои можат да бидат лесно иретуларни.За аквирираните невуси се смета дека се развиле од епидермалните меланоцити кои ја завршиле својата миграција од неуралнио срт во дермо-епидермалната јункција во феталниот развој или се создале од дермо-епидермалните меланоцити кои биле заробени во дермисот.5

Аквирираните невуси се поделени на ;

јункционални-клетките се на дермо-епидермалната јункција

дермални-клетките се наоѓаат во дермисот

мешани-клетките се наоѓаат и во епидермис и дермис.6

Бројот на аквирираните невуси може да варира од неколку до стотици.Преваленцата на АН е поголема кај кавкаскиот тип на луѓе посебно тие со бел тен и кај нив АН се лоцирани на телото и фотоекспонираните регии за разлика од азијатите каде невусите се наоѓаат почесто на акралните делови од телото(екстремитети,дланки и стапала.)

Покачен број на АН се опсервираат во одредени фамилии.Силнопозитивнакорелацијаедетерминирана помеѓу сончевата експозиција и бројот на невуси.АН имаат низок малиген потенцијал,секако асоцијацијата помеѓу аквирираните невуси и меланомот постои. Хистолошките стадиуми покажуваат дека 1/3 од меланомите се асоцирани со аквирирани невуси.

Клинички АН се презентираат како асимптоматски,округли или овални,во дијаметар помали од 1см со регуларни или лесно иретуларни граници,во однос на бојата светло до темно кафени. АН може да се јават насекаде по телото.

Јункционалните невуси-се презентираат како макуларни лезии најчесто лоцирани на трупот горните екстремитети и лицето.

Мешаните невуси-се лесно елевирани папуларни лезии со мазна или лесно верукозна површина ,темно кафена до црна боја.Лицето е најчеста локализација на овие невуси.

Дермалните невуси – се папиломатозни или нодуларни,округли .Тие имаат светло кафена боја,кај нив се присатни телеангиектазии.Лоцирани се на лицето ,вратот и телото.

Класификација на невуси базирана на дермоскопија

Непостоењето на консензус помеѓу клиничарите и патолозите,поради мешаните клинички и

хистопатолошки структури за да се класифицираат меланоцитните невуси,води до постојано барање на нови класификации.Дермоскопските структури кај меланоцитните невуси корелираат со специфичните хистопатолошки структури.На основа на ова се правени повеќе класификации на меланоцитните од кој ке бидат опишани две.Класификацијата на невусите води до нивно полесно дијагностицирање и полесно диференцирање од меланомот.7

Практицирањето на дермоскопијата им овозможува на клиничарите да ги набљудуваат и структурите и боите кои не можат да ги видат со голо око.

Сите овие структури и бои имаат свои хистопатолошки корелации.Не е за изненадување фактот што е добиен од повеќебројни студии во кои е утврдено дека дермоскопијата го зголемува процентот на точноста на дијагнозата на пигметните лезии .

Покрај ова дермоскопијата и дигиталната дермоскопија овозможува следење на еволуцијата и промените во невусите,кое допринесува за знаења и во делот на невогенезата.8

Новата класификација на Меланоцитните невуси е базирана на дермоскопските шеми во корелација со епидемологијата,клинички и хистопатолошките критериуми.Овој систем на класификација е дизајниран за клиничарите кој се баваат со дијагноза и менаџмент на меланоцитните кожни лезии.

Друга дермоскопска класификација на меланоцитните лезии ги дели спрема структурата

(глобуларни, глобуларно-ретикуларни, глобуларно-хомогена, ретикуларна, ретикуларно хомогена, хомогена). 9

Во однос на пигментацијата (униформна, централна–хиперпигментација, централнии–хипопгментациј, ексцентрична-хиерпигментација, ексцентрична-хипопигментација, мултифокална–хипо-хиперпигментација.

Во однос на бојата (бела, црвена, светло-кафена, темно-кафена, плава, сива и црна).

Класификација дермоскопска по која ќе се работи корелацијата на возраста и анатомската регија во оваа студија е следнава:

Г-глобуларен

Р-ретикуларен

МП-мешан со мрежа во периферијата

МГ-мешан со глобули во периферијата

Н-неспецифичен

МАТЕРЈАЛ И МЕТОДИ

Спрема дизајнот ќе се изработи опсервациона пресечна студија.

Во истражувањето ќе се почитуваат етичките начела на Хелсиншката декларација на Светската Медицинска Асоцијација,Belmont извештајот и UNESCO-вата Универзална декларација за биоетика и човекови права.

Студијата ќе се одвива на Клиниката за Дерматовенерологија почнувајќи од Ноември 2017 год.

Вкупно ке бидат вклучени 400 испитаници,поделени во 8 групи спрема возраст(2-10,11-20,21-30,31-40,41-50,51-60,61-75,над 75год.) ,со минимум 50 иситаници во група и минимум 5 невуси,со што се добива број од минимум 2000 анализирани невуси.

Бидејќи ке се анализираат аквирираните невуси нивната дермоскопска поделба на подтипови спрема морфологија е следната

1.Униформна глобуларна структура (Г)

2.Униформна ретикуларна структура(Р)

3.Мешана структура составена од централна глобуларна структура или безструктурна,во периферија опкружена со пигментна мрежа (МП)

4.Мешана структура составена од централно мрежа или безструктурна,а во периферија опкружена со глобули(МГ)

5.Неспецифична структура (Н)

А) Инклузиони критериуми за вклучување во студијата

-Возраст над две години(поради тоа што се анализираат аквирирани невуси)

-Пациенти кои имаат барен 5 невуси на телото

кои се со големина од 2мм-2см

-Пациенти со минатa лична и семејна анамнеза за меланом

Б)Ексклузиони критериуми за студијата

-Пациенти на возраст под две години

-Невуси со големина над 2см

Како метод се употребува дермоскопија при што се анализираат невусите на телото и главата со исклучок на дланките и табаните кои имаат различна морфологија поради специфичноста на анатмските регии. Исто така не се анализираат и невуси на семимукози и мукози.

ЦЕЛИ

Цели на студијата е утврдување дали постои корелација помеѓу различните демоскопски типови на невуси во зависност од возраста.

РЕЗУЛТАТИ

Во нашето истражување се потврди сигнификантно различна застапеност на одделни морфолошки типови на невуси кај испитаниците на различна возраст.

Невуси со униформна глобуларна структура беа почесто детектирани кај помладите возрасни групи, односно кај 98% (49) испитаници на возраст од 2 до 10 години, кај 88%(44) испитаници на возраст од 11 до 20 години, кај половина испитаници во возрасната група од 21 до 30 години, кај 42%(21) испитаници на возраст од 31 до 40 години, кај 30%(15) испитаници на возраст од 41 до 50 години, кај 46%(23) испитаници во возрасната група од 51 до 60 години, и кај 24%(12) испитаници помеѓу 61 и 75 години. Г невуси не беа дијагностицирани кај пациентите постари од 75 години.

Статистичка сигнификантна разлика се потврди во зачестеноста на Г невуси кај испитаници на различна возраст (p<0.0001).

Овој морфолошки тип на невуси значајно почесто беше дијагностициран кај испитаниците на возраст од 2 до 10 години споредено со останатите возрасни групи, кај испитаниците на возраст од 11 до 20 години споредено со останатите возрасни групи, кај испитаниците на возраст од 21 до 30 години споредено со оние на возраст од 41 до 50 години, и постари од 61 година, кај испитаниците на возраст од 31 до 40 години споредено со испитаниците постари од 61 година, кај испитаниците на возраст од 41 до 50 години споредено со постари од 75 години, и кај испитаници на возраст од 61 до 75 години компарирани со испитаници над 75 годишна возраст. (табела 1и 2.)

Табела 1

невус Г	возрасни групи								
	n	2–10 n (%)	11–20 n (%)	21-30 n (%)	31-40 n (%)	41-50 n (%)	51-60 n (%)	61-75 n (%)	>75 n (%)
да	189	49(98)	44(88)	25(50)	21(42)	15(30)	23(46)	12(24)	0
не	211	1(2)	6(12)	25(50)	29(58)	35(70)	27(54)	38(76)	50(100)
p-level	Pearson Chi-square X2=147.32 p=0.000000 sig								

Табела 2

невус Г							
возрасни групи	возрасни групи						
	11–20	21-30	31-40	41-50	51-60	61-75	>75
2–10	NS	p=0.00000	p=0.00000	p=0.0000	p=0.0000	p=0.0000	p=0.00000
11–20		p=0.0000	p=0.000001	p=0.00000	p=0.000008	p=0.0000	p=0.0000
21-30			NS	p=0.041	NS	p=0.007	p=0.0000
31-40				NS	NS	p=0.0056	p=0.0000003
41-50					NS	NS	p=0.000027
51-60						p=0.021	p=0.0000
61-75							p=0.00022

Испитаниците од повозрасните групи почесто од помладите испитаници имаа невуси со униформна ретикуларна структура. Р тип на невуси беа дијагностицирани кај сите 50 испитаници постари од 75 години, кај 92% (46) на возраст од 61 до 75 години, кај 94% (47) на возраст од 51 до 60 години, и кај исто толку испитаници на возраст од 41 до 50 години. Во возрасната група испитаници од 31 до 40 години Р невуси имаа 88% (44) испитаници, а 74% (37) во возрасната група од 21 до 30 години. Само 16% (8) испитаници од најмладата возрасна група имаа Р невуси.

Статистичката анализа како сигнификантна ја потврди разликата во зачестеноста на Р невуси кај испитаници Табела 3

невус Р	возрасни групи								
	n	2–10 n (%)	11–20 n (%)	21-30 n (%)	31-40 n (%)	41-50 n (%)	51-60 n (%)	61-75 n (%)	>75 n (%)
да	307	8(16)	28(56)	37(74)	44(88)	47(94)	47(94)	46(92)	50(100)
не	93	42(84)	22(44)	13(26)	6(12)	3(6)	3(6)	4(8)	0
p-level	Pearson Chi-square X2=157.57 p=0.000000 sig								

Табела 4

невус Р							
возрасни групи	возрасни групи						
	11–20	21-30	31-40	41-50	51-60	61-75	>75
2–10	p=0.00003	p=0.0000	p=0.0000	p=0.0000	p=0.0000	p=0.0000	p=0.0000
11–20		NS	p=0.00037	p=0.000011	p=0.000011	p=0.0000	p=0.0000
21-30			NS	p=0.0064	p=0.0064	p=0.017	p=0.0001
31-40				NS	NS	NS	Fisher p=0.027
41-50					NS	NS	NS
51-60						NS	NS
61-75							Fisher p=0.012

Невуси со мешана структура, централно глобуларна или без структура, во периферија со пигментна мрежа, најчесто беа детектирани кај испитаници на возраст од 41 до 50 години, и од 21 до 30 години – 58% (29) и 54% (27) испитаници консеквентно.Ваков тип на невуси имаа 22% (11) испитаници од најмладата возрасна група, а само 6% (3) од најстарата возрасна група.

За вредност на p<0.0001 се потврди сигнификантна разлика меѓу испитаниците на различна возраст, а во однос на зачестеноста на МП тип на невуси.

Меѓугрупните тестирања покажаа дека оваа вкупна сигнификантност се должи на: значајно поретко дијагностицирање на овој тип невуси кај испитаниците на возраст од 2 до 10 години споредено со испитаници на возраст од 21 до 30 години, и од 51 до 60 години, а значајно почесто во однос на најстарите испитаници; на значајно поретко дијагностицирање кај испитаниците на возраст од 11 до 20 години споредено со испитаниците на возраст од 21 до 30, и од 41 до 50 години; на значајно почесто дијагностицирање кај испитаниците на возраст од 21 до 30 години, споредено со испитаници на возраст од 31 до 40, и кај испитаници постари од 51 година; на значајно поретко дијагностицирање кај испитаници на возраст од 31 до 40 години споредено со испитаници на возраст на различна возраст (p<0.0001).

Меѓугрупните споредби покажаа дека Р тип на невуси значајно поретко беше дијагностициран кај испитаниците на возраст од 2 до 10 години споредено со останатите возрасни групи, кај испитаниците на возраст од 11 до 20 години споредено со испитаниците на возраст над 31 година, кај испитаниците на возраст од 21 до 30 години споредено со испитаниците постари од 41 година, кај испитаниците на возраст од 31 до 40 години споредено со испитаниците постари од 75 години, и кај испитаници на возраст од 61 до 75 години спредено со испитаници над 75 годишна возраст. (табела 3 и 4)

од 41 до 50 години,а значајно почесто од најстарите испитаници; на значајно почесто дијагностицирање кај испитаниците на возраст од 41 до 50 години во однос на испитаниците постари од 51 година; на значајно почесто дијагностицирање кај испитаниците на возраст од 51 до 60, и од 61 до 70 години во однос на испитаници постари од 75 година. (табела 5 и 6.)

Табела 5.

невус МП	возрасни групи								
	n	2–10 n (%)	11–20 n (%)	21-30 n (%)	31-40 n (%)	41-50 n (%)	51-60 n (%)	61-75 n (%)	>75 n (%)
да	111	11(22)	7(14)	27(54)	14(28)	29(58)	10(20)	10(20)	3(6)
не	289	39(78)	43(86)	23(46)	36(72)	21(42)	40(80)	40(80)	47(94)
p-level	Pearson Chi-square X2=60.34 p=0.000000 sig								

Табела 6.

возрасни групи	возрасни групи						
	11–20	21-30	31-40	41-50	51-60	61-75	>75
2–10	NS	p=0.00098	NS	p=0.00024	NS	NS	p=0.021
11–20		p=0.000024	NS	p=0.0000046	NS	NS	NS
21-30			p=0.008	NS	p=0.00043	p=0.00043	p=0.0000002
31-40				p=0.0025	NS	NS	p=0.0034
41-50					p=0.000098	p=0.000098	p=0.0000
51-60							p=0.037
61-75							p=0.037

Зачестеноста на невуси со мешана структура со централна мрежа или без структура, а во периферија глобули, сигнификантно се разликуваше кај испитаниците на различна возраст (p<0.0001). Дистрибуцијата на овој тип невуси во 8-те возрасни групи покажува нивна застапеност кај 30% (15) испитаници на возраст од 2 до 10 години, 48% (24) на возраст од 11 до 20 испитаници, кај 32% (16) испитаници на возраст од 21 до 30 години, кај 22% (11) испитаници на возраст од 31 до 40 години, кај 46% (23) испитаници на возраст од 41 до 50 години, и кај еден испитаник во возрасната група од 61 до 75 години. Кај испитаниците на возраст од 51 до 60 години, и постари од 75 години не беше дијагностициран МТ тип на невус.

Меѓугрупните споредби покажаа дека МТ тип на невуси значајно почесто беше дијагностициран кај испитаниците на возраст од 2 до 10 години споредено со испитаниците постари од 51 година; кај испитаниците на возраст од 11 до 20 години споредено со испитаниците на возраст од 31 до 40 години и постари од 51 година; кај испитаниците на возраст од 21 до 30 години споредено со испитаниците постари од 51 година; значајно поретко кај испитаниците на возраст од 31 до 40 години споредено со испитаниците на возраст од 41 до 50 години, а значајно почесто од испитаниците постари од 51 година; и значајно почесто кај испитаниците на возраст од 41 до 50 години споредено со испитаници постари од 51 година. (табела 7 и 8)

Табела 7.

невус МТ	возрасни групи								
	n	2–10 n (%)	11–20 n (%)	21-30 n (%)	31-40 n (%)	41-50 n (%)	51-60 n (%)	61-75 n (%)	>75 n (%)
да	90	15(30)	24(48)	16(32)	11(22)	23(46)	0	1(2)	0
не	310	35(70)	26(52)	34(68)	39(78)	27(54)	50(100)	49(98)	50(100)
p-level	Pearson Chi-square X2=79.77 p=0.000000 sig								

Табела 8.

возрасни групи	возрасни групи						
	11–20	21-30	31-40	41-50	51-60	61-75	>75
2–10	NS	NS	NS	NS	p=0.00003	p=0.00013	p=0.00003
11–20		NS	p=0.006	NS	p=0.0000	p=0.0000001	p=0.000000
21-30			NS	NS	p=0.000013	p=0.000065	p=0.000013
31-40				p=0.011	p=0.00044	p=0.002	p=0.00044
41-50					p=0.0000	p=0.0000003	p=0.0000
51-60						NS	
61-75							NS

Невуси со неспецифична структура најчесто беа детектирани кај испитаници на возраст од 21 до 30 години – 52% (26), а потоа кај испитаници на возраст 61 до 75 години – 44% (22).Ваков тип на невуси не беа дијагностицирани во најмладата возрасна група испитаници, а ги имаа 6% (3) испитаници постари од 75 години.

За вредност на p<0.0001 се потврди сигнификантна разлика меѓу испитаниците на различна возраст, а во однос на зачестеноста на H тип на невуси.

Меѓугрупните тестирања покажаа дека оваа вкупна сигнификантност се должи на: значајно поретко дијагностицирање на овој тип невуси кај испитаниците на возраст од 11 до 20 години споредено со испитаници на возраст од 21 до 30 години, а значајно почесто во однос на најстарите испитаниици; на значајно почесто дијагностицирање кај испитаниците на возраст од 21 до 30 години споредено со испитаниците на возраст од 31 до 60 години, и постари од 75 години; на значајно поретко дијагностицирање кај испитаниците на возраст од 31 до 40 години и 41 до 50 години споредено со испитаници на возраст од 61 до 70, а значајно почесто од најстарите испитаници; на значајно почесто дијагностицирање кај испитаниците на возраст од 51 до 60, и од 61 до 70 години во однос на испитаници постари од 75 година.(Табела 9 и 10)

Табела 9.

невус H	возрасни групи								
	n	2–10 n (%)	11–20 n (%)	21-30 n (%)	31-40 n (%)	41-50 n (%)	51-60 n (%)	61-75 n (%)	>75 n (%)
да	101	0	13(26)	26(52)	11(22	12(24)	14(28)	22(44)	3(6)
не	299	50(100)	37(74)	24(48)	39(78)	38(76)	36(72)	28(56)	47(94)
p-level	Pearson Chi-square X2=55.51 p=0.000000 sig								

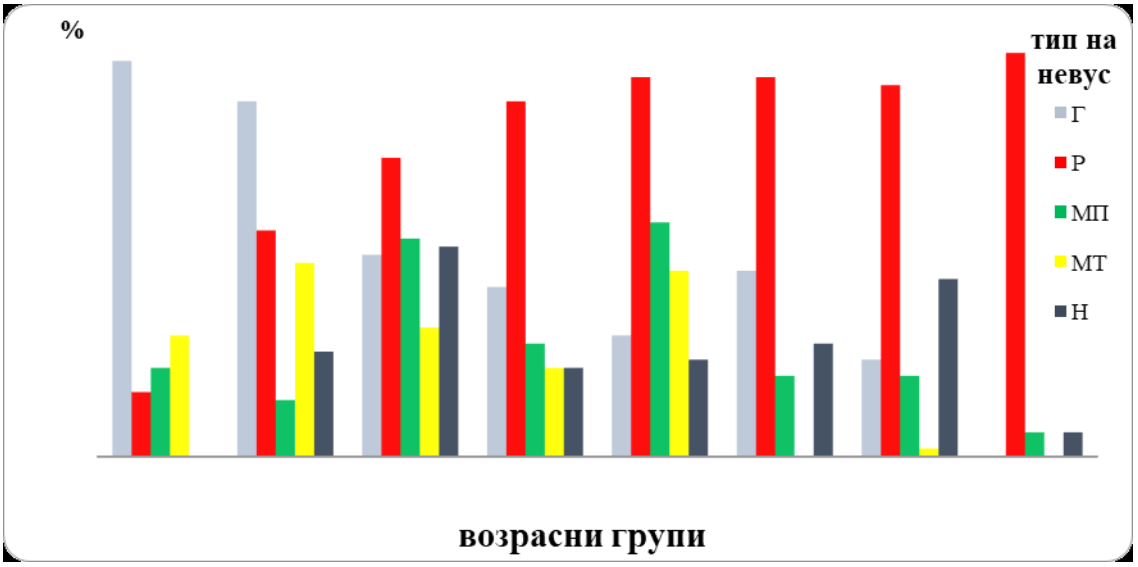
Табела 10.

возрасни групи	возрасни групи						
	11–20	21-30	31-40	41-50	51-60	61-75	>75
2–10	p=0.00011	p=0.0000	p=0.00044	p=0.00022	p=0.000055	p=0.0000001	NS
11–20		p=0.0077	NS	NS	NS	NS	p=0.0064
21-30			p=0.0019	p=0.0039	p=0.014	NS	p=0.0000004
31-40				NS	NS	p=0.019	p=0.021
41-50					NS	p=0.035	p=0.012
51-60						NS	p=0.0034
61-75							p=0.000011

Во табела 11 прикажана е застапеноста на 5-те морфолошки типови невуси кај испитаниците од 8-те возрасни групи.

Табела 11.

тип на невус	возрасни групи								
	n	2–10 n (%)	11–20 n (%)	21-30 n (%)	31-40 n (%)	41-50 n (%)	51-60 n (%)	61-75 n (%)	>75 n (%)
Г	189	49(98)	44(88)	25(50)	21(42)	15(30)	23(46)	12(24)	0
Р	307	8(16)	28(56)	37(74)	44(88)	47(94)	47(94)	46(92)	50(100)
МП	111	11(22)	7(14)	27(54)	14(28)	29(58)	10(20)	10(20)	3(6)
МТ	90	15(30)	24(48)	16(32)	11(22)	23(46)	0	1(2)	0
Н	101	0	13(26)	26(52)	11(22	12(24)	14(28)	22(44)	3(6)



Графикон 1.Застапеност на дермоскопските типови на невуси во зависност од возраста

ДИСКУСИЈА

Различните типови на меланоцитни невуси постојат и се во релација со еволуцијата,морфологијата,генетика та и нивната асоцираност со појавата на меланомот.Тоа го потврдуваат дел од студиите кој се работени на оваа тема10,11,12 од кои што произлегуваат и заклучоците за двете патеки на развој кои влијаат на формирање на невусите ендогена и егзогена.Лонгитудиналните студии нудат повисок степен на доказ кај овој тип на истражувања.

Развојот на дермоскопијата како метода отвара нова морфолошка димензија на меланоцитните невуси,како и подобро разбирање на нивната молекуларна структура и можност за нови класификации13. Нејзината релевантност како метода во ваков тип на иследувања е потврдена со студиите за ефикасност на дермоскопијата во дијагноза на пигментните лезии,сензитивност и специфичност14,15 {53,54}.

Базирано на дефиниција аквирирани меланоцитни лезии се сите бенигни лезии кои се јавуваат на кожата по раѓањето.За разлика од конгениталните кај кои ризикот за развој на меланомот зависи од големината ,кај аквирираните невуси клучни фактори за асоцијација со меланомот од досегашните студии се бројот и варијабилноста во морфологијата16.

Со оглед на широката морфолошка хетерогеност на оваа група не изненадува тоа дека класификацијата на аквирираните невуси е различна17,18

Базирано на нашата лимитираност за клиничка диференцијација помеѓу различните невуси.Дури и хистопатологијата која претставува златен стандард за дијагноза и класификација, во овој случај има лимитираност,најпрвин поради селекционио бијас и поради тоа што невусот се анализира во една точка од времето ,а тоа го оневозможува следењето на еволуцијата и инволуцијата.

Фактот дека дермоскопијата овозможува визуелизација на лезии кои не се видливи со голо

око,како и тоа дека визуелзираните струкури имаат свои хистопатолошки еквиваленти, ја прави метода релевантна за опсервација на морфолошката разноликост на невусите и нивната промена со текот на времето19,20

Всушност тука е главната улога ја има дермоскопијата да претставува мост помеѓу макроскопскиот и микроскопскиот свет и да води до нивна интеграција. Дермоскопската дијагноза се базира на четири варијабли:1.морфологија 2.пигментација 3.боја 4.специфични локализации.

Во оваа студија се користат класификациите по морфологија и пигментација и се корелираат со останатите параметри (анатомска регија,возраст,фототип).

Оваа студија укажува на тоа дека постои сигнификантна разлика помеѓу различните дермоскопски типови кај одредени возрасти.

Во детската возраст поточно од 2-10 г доминантен тип на невус беше глобуларниот невус ,кој процентуално најзастапен беше во првите 2 групи,додека во последната група на 75 г воопшто е се појавува.

За разлика од Ретикуларниот невус кој предоминантно се јавува во повозрасната популација и кај голем дел и над 75 годишна возраст.

МГ (мешан невус со глобули на периферијата) всушност е сигнификантен за помалата возраст,всушност и неговото присуство не е забележано во највозрасните групи.Овој невус и во литературата во следните студии 18,19 е опишан како растечки невус кој се среќава во помладата популација,ова забележување може да има практична примена во менацментот на овие лезии кај повозрасни од 30 години да се опсервираат со посебен акцент,да се направи и дигитална дермоскопија овие периферни глобули може да бидат знак за меланом кај возрасната популација.21

Студиите кој ги проучуваат дермоскопските типовите на невуси можат да дадат допринос во изработка на попрецизни дијагностички алгоритми како и предктивни модели за попорецизна дијагноза во однос на пигментите тумори.

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Original scientific paper

PERIOPERATIVE CHARACTERISTICS IN DIABETIC VS. NON DIABETIC PATIENTS UNDERGOING CORONARY ARTERY BYPASS SURGERY

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ABSTRACT

Objectives: This study aims to compare the perioperative clinical, angiographic and operative characteristics and early complications of diabetic patients with non-diabetic patients, undergoing isolated CABG at the University Hospital for Cardiac Surgery in Skopje. Methods: During the period from October 2017 to October 2018, ninety one consecutive patients undergoing CABG were enrolled in this prospective observational study. This population was then divided into those with DM and those without DM. For these groups, preoperative clinical, angiographic, intraoperative characteristics and postoperative complications were evaluated. Results: In our cohort, 48, 4% of the patients were diabetic. Except for smoking, all other risk factor were evenly distributed between the two groups. Patients with DM had similar SYNTAX score like non-diabetic patients (31, 7±5, 5 vs. 30, 3±7, 2, p=0,312). Patients with DM had higher No of diseased vessels (2, 9±0, 7 vs. 2, 5±0, 6, p=0,020), less LM disease (22, 7% vs. 42, 6% p=0,036). There was no statistical difference between the two groups in terms of intubation time (p=0,137), inotropic support (p=0,774) and vasopressor support (p=0,076). Diabetic patients had less re-sternotomies (p=0,066) than non-diabetic patients. Postoperative AF, perioperative MI, stroke, sternal wound infection and leg wound infection were similar in both groups. Length of hospital stay was 9 days in both groups. Conclusion: Our data do not support the conclusions by other authors who found diabetes to be a risk factor for significantly adverse early morbidity following CABG. In our study DM was not risk factor for perioperative complications and preoperative characteristic of diabetic patients were not different than in no diabetic

INTRODUCTION

It is now widely accepted that worldwide diabetes prevalence is surpassing even the most pessimistic projections from the past. For example, in 2004, it was estimated that diabetes prevalence in 2030 would reach 334 million people, whereas the actual prevalence of 387 million people with diabetes was already reached in 2014, and the new projection for 2035 is 592 million, almost double what was estimated only 10 years ago (1,2). In Republic of North Macedonia (RNM), the estimated total diabetes prevalence in 2014 was 180,180 (90,020 men and 90,160 women). RNM has a national diabetes prevalence of 11.44%, which is the third highest in Europe, behind just Turkey and Montenegro, and a comparative (age-adjusted) diabetes prevalence of 9.76%, or the second highest in Europe, after Turkey (2). Clinically, coronary atherosclerosis is worse in every measurable way in patients with diabetes mellitus (DM) as manifested by early and more diffuse atherosclerosis producing a greater disease burden, more frequent left main coronary

stenosis and multivessel disease, more total occlusions, and an impaired ability to develop collateral circulation (3,4). The net clinical effect more than doubles the risk of coronary artery disease (CAD) in patients with DM, and the disease is lethal: ischemic CAD causes three quarters of DM-related deaths (5)

Coronary artery bypass grafting (CABG) is nowadays the preferable revascularization treatment in diabetic patients over percutaneous coronary interventions (PCI) (6, 7). PCI and CABG uncovered the unique biology of diabetic vascular disease and patients with DM continued to face worse outcomes, mortality, and complications than similar patients without DM (8, 9).

Several studies revealed different preoperative clinical characteristics, higher morbidity and perioperative mortality rates among patients with DM vs. non-diabetic patients undergoing CABG (10-12). This finding is probably related to the occurrence of perioperative myocardial infarction, infections, respiratory failure, renal and cerebral complications, all of which prolong hospitalization and worse outcome in these patients. Moreover, the presence of DM is considered to be an independent risk factor for postoperative mortality after CABG (10)

This study aims to compare the perioperative clinical, angiographic and operative characteristics and early complications of diabetic patients with non-diabetic patients, undergoing isolated CABG at the University Hospital for Cardiac Surgery in Skopje – RNM

METHODS

Study patients.

During the period from October 2017 to October 2018, ninety one consecutive patients undergoing CABG were enrolled in this prospective observational study. Patients were included in the database if they fulfilled the following inclusion criteria: they were consecutive patients aged 18 years or older (no restrictions on sex or nationality) and had undergone CABG. All procedures were done on-pump with cardiopulmonary bypass (CPB). We used Thomas crystalloid cardioplegia. Except in 5 patients, left or right internal thoracic artery (LITA or RITA) was used to bypass the left anterior descending artery (LAD). None of the patients had associated surgical procedures such as valve replacement or aortic surgery. This population was then divided into those with DM and those without DM. For these groups, preoperative clinical and angiographic characteristics, intraoperative characteristics and postoperative complications were evaluated. Among the clinical complications that occurred following CABG, the following variables were analyzed: perioperative acute myocardial infarction (AMI), neurological complications, pulmonary complications, renal complications, infectious complications, cardiac arrhythmias and multiple organ failure occurring within 30 days after the surgery. This study was approved by the Medical Ethics Committee of Medical School, University "St.Cyril&Methodius, Skopje, and all patients provided informed consent.

STATISTICAL ANALYSIS

Categorical parameters were summarized as percentages and continuous parameters as mean ±SD. Continuous variables were compared using nonparametric Mann-Whitney test for independent samples and categorical parameters were compared using Pearson's chi square test. All data analysis was performed using SPSS version 25.0 (IBM SPSS, Inc., Chicago, Illinois) and p value ≤ 0.05 was considered significant.

RESULTS

The patients were divided into two subgroups: those with DM (n=44/48, 4%) and those without DM (n=47/51, 6%). The baseline demographic and clinical characteristics of the 91 patients as a whole and divided into subgroups, including preoperative risk factor are shown in Table 1 and were similar in both subgroups. Diabetic patients were 3 years older than non-diabetics (p=0, 07). Except for smoking (more prevalent in the non-diabetic group, 57, 4% vs. 38, 6%, p=0, 05) all other risk factor were evenly distributed between the two groups. Patients with diabetes had slightly higher percent of PVD and CVI, and diabetic patients had slightly higher percentage of significant carotid disease, but this results didn't reach statistical significance. Patients with diabetes had higher Euro SCORE (2, 5 vs. 1, 5).

Table 1. Baseline characteristics in the study population as a whole and comparison of demografic, clinical and echocardiograpfic characteristics of 91 patients divided according to the presence of DM.

Parameter (n/%)	All patients 91	DM 44/48,4	No DM 47/51,6	p
Age (years)	65,4±7,9 43-82	66,9±6,8	63,9±8,6	0,072
Gender (n/%) Male Female	70/76,9 21/23,1	35/79,5 9/20,5	35/74,5 12/25,5	0,931
BMI (kg/m2)	27,5±4,2	28,0±3,9	27,1±4,5	0,308
Euro SCORE	2,0±1,5	2,5±1,6	1,5±1,2	0,003
NYHA (n/%)	2,2±0,5	2,3±0,6	2,1±0,5	0,213
CCS (n/%)	2,3±0,5	2,4±0,5	2,3±0,5	0,228
Angina, stable (n/%)	47/51,6	19/43,2	28/59,6	0,088
Previous MI (n/%)	38/41,8	19/43,2	19/40,4	0,478
Previous PCI (n/%)	17/18,7	9/20,5	8/17,0	0,440
Urgent CABG (n/%)	29/31,9	17/38,6	12/25,5	0,132
Smoking (n/%)	44/48,4	17/38,6	27/57,4	0,056
Hypertension (n/%)	88/96,7	43/97,7	45/95,7	0,525
Dyslipidemia (n/%)	85/93,4	40/90,9	45/95,7	0,307
Preoperative AF (n/%)	10/9,1	4/9,1	4/8,5	0,605
COPD (n/%)	14/15,6	7/15,9	7/15,2	0,578
PVD (n/%)	20/21,1	7/15,9	10/21,3	0,350
Carotid disease	17/18,2	8/17,0	12/13,2	0,405
CKD (n/%)	26/28,6	13/29,5	13/27,7	0,513
CVI (n/%)	12/13,2	5/11,4	7/14,9	0,427

CABG = coronary artery bypass graft surgery; BMI = body mass index; MI=myocardial infarction; PCI=percutaneous coronary intervention; AF=atrial fibrillation; COPD= chronic obstructive pulmonary disease; PVD=peripheral vascular disease; CKD=chronic kidney disease;

Angiographic and intraoperative characteristics in the study population as a whole and divided according to the presence of DM are shown in table 2. Patients with DM had similar SYNTAX score like non-diabetic patients (31, 7±5, 5 vs. 30, 3±7, 2, p=0,312). Patients with DM had higher No of diseased vessels (2, 9±0, 7 vs. 2, 5±0, 6, p=0,020), less LM disease (22, 7% vs. 42, 6% p=0,036), and similar distribution of 1, 2 and 3 vessel disease (p=0,260) like patients without DM.

Patients with DM got more distal anastomoses than non-diabetics (2, 9±0, 7 vs. 2, 5±0, 6 p=0,002), and more diabetic patients got three distal anastomosis (70, 5% vs. 48, 9%). Utilization of type of the grafts (LITA, RITA, venous, RA or NTSVG) was even between two groups. Diabetic patients had slighter longer bypass time and cross clamp time than non-diabetics, but that didn't reach statistical significance (p=0,263 and p=0,142)

Table 2. Angiographic and intraoperative characteristics in the study population as a whole and divided according to the presence of DM.

Parameter (n/%)	All patients 91	DM 44/48,4	No DM 47/51,6	p
SYNTAX score	31,0±6,4	31,7±5,5	30,3±7,2	0,312
No of diseased vessels	2,8±0,4	2,9±0,7	2,5±0,6	0,020
Left main disease	30/33,0	10/22,7	20/42,6	0,036
LAD proximal disease	69/75,8	34/77,3	35/74,5	0,474
1 vessel disease 2 vessel disease 3 vessel disease	1/1,1 15/16,5 75/82,4	0 5/11,4 39/88,6	1/2,1 10/21,3 36/76,6	0,260
Number of distal anastomosis	2.7±0.7	2,9±0,7	2,5±0,6	0,002
Number of distal anastomosis per patient (n/%) 1 2 3 4 5	 4/44 25/27,5 54/59,3 6/6,6 2/2,2	 2/4,5 6/13,6 31/70,5 3/6,8 2/4,5	 2/4,3 19/40,4 23/48,9 3/6,4 0	0.043
LITA/RITA (n/%) Only venous (n/%) RA (n/%) NTSVG (n/%)	86/94,5 5/5,5 6/6,7 18/19,8	41/93,1 3/6,8 4/9,1 8/18,2	45/95,7 2/4,2 2/4,3 11/23,4	0,367 0,450 0,307 0,362
CPB time (min)	107,1±28,1	110,4±29,6	103,7±26,4	0,263
Ischemic time (min)	61,5±18,1	64,4±18,3	58,7±17,7	0,142

AF=atrial fibrillation; CPB=Cardio Pulmonary Bypass; LAD=Left Anterior Descending; PCI=percutaneous coronary intervention; LITA=left internal thoracic artery; RITA=right internal thoracic artery; RA=radial artery; NTSVG=no touch saphenous vein graft; SYNTAX= SYNergy between percutaneous intervention with TAXus drug-eluting stents and cardiac surgery;

The most important early postoperative parameters and complications are shown in table 3. There was no

statistical difference between the two groups in terms of intubation time (p=0,137), inotropic support (p=0,774), vasopressor support (p=0,076) and levels of high sensitive troponin after surgery. In terms of complications, diabetic patients had less re-sternotomies (p=0,066) than non-diabetic patients. Postoperative AF, perioperative MI, stroke, sternal wound infection and leg wound infection were similar in both groups and didn't reach statistical significance. Length of hospital stay was 9 days in both groups

Table 3. Postoperative course and early postoperative complications

Parameter (n/%)	All patients 91	DM 44/48,4	No DM 47/51,6	p
Intubation time (n/%) < 24 hours 24-72 hours > 72 hours	75/82,4 9/9,9 7/7,7	37/84,1 2/4,5 5/11,4	38/80,9 7/14,9 2/4,3	0.137
Inotropic support (n/%) No support <72 hours after CABG > 72 hours after CABG	50/54,9 33/36,3 8/8,8	24/54,5 17/38,6 3/6,8	26/55,3 16/34,0 5/10,6	0,774
Vasopressor support (n/%) No support First 72 hours More than 72 hours	34/37,3 50/54,9 7/7,8	19/45,2 22/52,4 3/6,8	13/27,7 28/59,6 5/10,6	0.076
hs-cTnT first post op day	4145,5±8219,6	4668,1±9947,9	3536,3±6061,2	0,542
Postoperative complications (n/%) AF Perioperative MI Stroke Revision (re-sternotomy) Sternal wound infection Leg wound infection Hemodialysis Reintubation	 33/36,3 2/2,2 3/3,3 7/7,8 2/2,2 4/4,4 1/1,1 9/10,0	 17/38,6 0 1/2,3 1/2,3 1/2,3 2/4,5 0 5/5,6	 16/34,0 2/2,2 2/4,3 6/12,8 1/2,1 2/2,2 1/2,1 4/4,4	 0,406 0,264 0,517 0,066 0,736 0,512 0,516 0,471
Length of hospital stay (days)	9,1±5,4	9,1±0,5	9,2±0,5	0,931

CABG=coronary artery bypass grafting; hs-cTnT=high sensitive troponin T; AF=atrial fibrillation

DISCUSSION

Almost half of the patients in our cohort were diabetics. Prevalence of diabetic patients in the largest CABG series in the literature varies between 11, 8% in the UK in 2000, to 40, 0% in the USA until 2009 (13, 14). Taking into account that diabetes prevalence of 9.76% in RNM is the second highest in Europe, after Turkey (2) it is no surprise that our cohort had more diabetic patients than the results in the literature. Despite our expectations that diabetic patients will have more preoperative risk factors in our study group, we didn't find any significant difference between the two groups. In their study Yamaguchi et al. (15) compared the perioperative characteristics, in-hospital outcomes and long-term outcomes between diabetic (n = 1110) and non-diabetic patients (n = 1508). They found that obesity, hypertension, dyslipidemia, peripheral artery disease and chronic kidney disease were significantly more prevalent in diabetic patients than in non-diabetic patients.

Mean SYNTAX score was insignificantly different between the two groups (31, 7 vs. 30, 3 p=0,312), and although this result seems unusual because of the diffuse nature of the atherosclerosis in diabetic patients, this finding was confirmed in other studies (16, 17). Triple-vessel disease was more prevalent in the diabetes group than in the non-diabetes group. As a consequence, the number of distal anastomoses was significantly higher in the diabetes group. Higher number of distal anastomoses in diabetic vs non-diabetic patients was confirmed in other studies (18, 19) and the reason for that is the need for complete revascularization in more diffusely diseased coronary arteries.

Although many previous studies have documented a higher incidence of postoperative adverse events (20) and poorer long term survival in diabetic patients than in non-diabetic patients, CABG has been regarded as the preferred revascularization strategy for diabetic patients with multivessel coronary artery disease, owing to a demonstrable survival advantage and reduced need for repeat revascularization (21). In this series, the incidence of morbidity events analyzed were similar in the two groups by univariate analysis, with only re-sternotomy showing higher incidence in non-diabetic patients. This finding is also in accordance with those of some recent studies (22). In contrast with the previously published studies of Rajakaruna, Kubal and their co-workers (23, 24), we could not identify diabetes as an independent predictor of acute renal failure or prolonged length of stay. Additionally, diabetes was also not associated with the rate of postoperative myocardial infarction, with increased requirement for inotropic or mechanical support and the occurrence of atrial arrhythmia. The

independent influence of diabetes in the development of a cerebrovascular accident has been described by some authors (23, 25). We didn't show higher incidence of cerebrovascular accidents by univariate analysis in our diabetic patients. This finding is also in accordance with those of some recent studies (24, 26).

LIMITATIONS

The limitation of this study is that it was an observational analysis, although the data were collected prospectively. At the time of data collection, this analysis had not been planned. It is possible that the differences or similarities observed between the groups were a result of unforeseen confounders. Also, this study was based on a small cohort of patients from a single institution, which limits its power. Hence, our data do not support the conclusions by other authors who found diabetes to be a risk factor for significantly adverse early outcome following CABG.

CONCLUSION

In conclusion, in our experience diabetic patients could be surgically revascularized with low morbidity rates, comparable to those of non-diabetic patients. Our data do not support the conclusions by other authors who found diabetes to be a risk factor for significantly adverse morbidity following CABG. In our study DM was not risk factor for perioperative complications and preoperative characteristic of diabetic patients were not different than in no diabetic

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Original scientific paper

DIAGNOSTIKIMI PRENATAL I KEQFORMIMEVE TË LINDURA TË ZEMRËS NË KOSOVË – PËRVOJË E SHKURTË NË KOSOVË

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HYRJE

Keqformimet e lindura të zemrës (KLZ) janë, pas keqformimeve të sistemit të traktit urinar, keqformimet më të shpeshta të trashëguara dhe, sipas statistikave të ndryshme, prekin 7 deri 10 fëmijë në 1000 lindje gjallë, ndërsa prevalenca është edhe më e lartë nëse do të përfshijnë KLZ-të tek abortet. Njëkohësisht, KLZ-të janë shkaku parësor i vdekshmërisë së fëmijëve në moshën neonatale dhe moshen e hershme latante.

Qëllimi i punimit: Është hulumtimi i sensitivitetit, specificitetit, vlerave prediktive pozitive dhe negative të ekokardiografisë fetale (FE) në diagnostikimin prenatal të keqformimeve të lindura të zemrës; me anë të rezultateve personale të japim përfundimet dhe qëndrimet tona në vlerësimin e mundësivë të ekokardiografisë fetale në zbulimin e llojit të çrregullimit të ritmt të zemrës, vlerësimin e suksesit të terapisë dhe parashikimin e përfundimit të shtatzënisë me keqformime të lindura të zemrës (KLZ) osë çrregullime të ritmit.

Qëllimi i punimit është edhe të prezantohen rezultatet e diagnositkimit prenatal të KLZ në Kosovë, patologjitë më së shpeshti të diagnostikuara si dhe ecurinë e fetuseve kardiopat.

Metodologjia Në mënyrë retrospektive janë prezantuar rezultatet e diagnostikimit prenatal ne Kosovë, mosha e shtatzënave në momentin e ekzaminimit, lloji i keqformimit të zemrës, ecuria e shtatzënisë si dhe menyra dhe vendi i lindjes.

Rezultatet Në periudhën kohore Janar 2017 – Dhjetor 201, janë ekzaminuar 205 fetuse nga 187 shtatzëni (14 shtatzëni gemelare, dy trinjake). Pjesa më e madhe e kzaminimeve është realizuar në Kliniken e Pediatrisë dhe Polikliniken "ECHO –SCAN" në Prishtinë. Një pjesë e vogël e ekzaminimeve është kryer në Qendrën Kryesore të Mjekësisë Familjare në Prishtinë. Gjithsej janë realizuar 342 ekokardiografi fetale. Çdo fetus është ekzaminuar 1 - 4 herë (mesatarisht 1.6± 0.6 herë). Ekzaminimi i parë është kryer në mes të javës 14-të dhe 38-të të shtatzënisë (mesatarisht në javët 25.9 ± 9.2). Sensitiviteti i EEF në grupin e fetuseve të studjuar ka qenë 91.67 % kurse specifiteti ka qenë 96.43 %. Vlera parashikuese pozitive ka qenë 84.62 % kurse vlera negative ka qenë 98.18 %. Rezultatet e ketij studimi janë në korelim të ngushtë me të dhënat nga literatura e cituar.

Konkludim Ekokardiografia fetale është metodë e sigurt, jo e rrezikshme dhe mjaft informative, me vlerë të paçmueshme në vlerësimin dhe diagnostikimin e sëmundjeve të lindura të zemrës.

Fjalët kyqe ekokardiografia fetale, diagnostikimi prenatal, keqformimet e lindura të zemrës,

HYRJE

Studimet e fundit tregojnë së diagnostikimi antenatal i KLZ-ve ka ndikim të rëndësishëm në uljen e sëmundshmërisë dhe vdekshmërisë nga keqformimet e komplikuara të zemrës. Ky diagnostikim mundëson trajtimin antenatal të disa KLZ-ve, planifikimin e lindjes, fillimin e trajtimit të të porsalindurit nga momenti i lindjes ose planifikimin e ndërhyrjeve kardio-kirurgjikale (ndërhyrjet paliative ose përfundimtare) menjëherë pas lindjes [1,2,3].

Ekokardiografia fetale nënkupton vlerësimin e zemrës përmes aplikimit të ultratingujve. Në implementimin dhe konfirmimin e menjëhershëm të kësaj metode në kardiologji dhe veçanërisht në kardiologjinë pediatrike dhe prenatale kanë kontribuar disa faktorë si: metoda është joinvazive dhe nuk shkakton dhimbje, mungesa e efekteve anësore biologjike, mundësia e përsëritjes, mundësia e përcjelljes dhe vlerësimit të efektit të terapisë, manipulimi relativisht i lehtë me një aparaturë me të cilën mund të ekzaminojmë pacientin edhe në njësinë e kujdesit intensiv dhe së fundi, mundësia e disponimit të këtij modaliteti diagnostik edhe nga qendra të mjekësore të vogla [4,5].

Ky screening përfshinë prezantimin e së paku dy prerjeve të zemrës së fetusit: prerjen katërhapësinore (four chamber view) dhe prerjen në nivel të tre enëve të gjakut (three vessel view) të cilat mundësojnë diagnostikimin e shumicës së KLZ-ve si në aspektin e keqformimeve të hapësirave të zemrës ashtu edhe atë të keqformimeve të enëve të mëdha të gjakut – keqformimet konotrunkale [6]. (Figura 1).

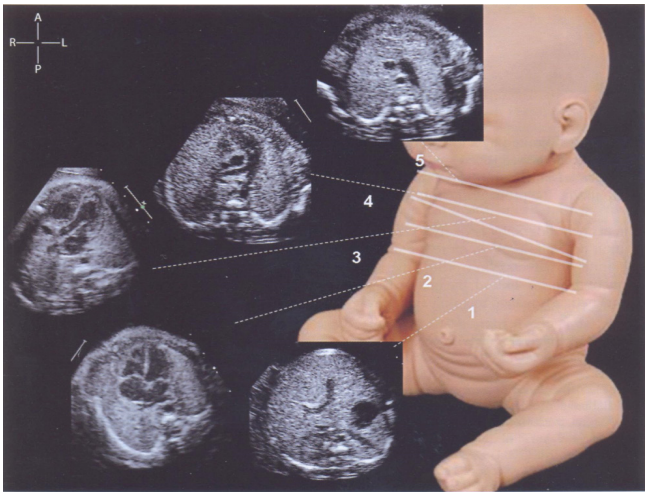


Figura 1. Përmbledhja e të gjitha prerjeve standarde

Ekzaminimi ekokardiografik fetal bëhet në institucionet lartë të specializuara dhe kërkon nga ekzaminuesi njohuri të lartë profesionale dhe njohuri të posacme të morfologjisë dhe patofiziologjisë së sistemit kardiovaskular të fetusit. Për këtë arsye, është e nevojshme të vendosen indikacionet e qarta për ekzaminimin ekokardiografik fetal (EEF) dhe të bëhet seleksionimi i fetuseve në shtatzënitë me risk të lartë [8].

Faktorët e rriskut mund të ndahen në dy grupe:

Në grupin e parë bëjnë pjesë shtatzënat me të ashtuquajturit "faktorë anamnestikë" të riskut, prania e të cilëve në mënyrë të shumfishtë rrit probabilitetin e KLZ-ve. Në grupin e dytë radhiten ndryshimet patologjike në shtatzëninë ekzistuese tek të cilat ekziston probabiliteti më i madh për konstatimin e keqformimeve të zemrës dhe për këtë arsye quhen "faktorë aktualë të riskut"[9,10].

Incidenca e KLZ te disa kromozomopati ose sindrome, që trashëgohen sipas ligjit të Mendelejevit, është e ndryshme dhe kap vlerën 14 % te sindromi Ellis Van Creveld deri në mbi 90% te trizomia 13-të dhe 18-të [11].

Sëmundjet e shtatzënës mund ta dëmtojnë SKV të neonatit me mekanizma që veprojnë në mënyrë direkte apo indirekte. Sëmundjet e nënës në mënyrë indirekte mund të dëmtojnë SKV të fetusit duke e kompromentuar qarkullimin utero-placentar. Ndër shumë faktorë patologjikë për nga rëndësia dhe shpeshtësia dallojmë dy faktorë: diabeti mellit i nënës dhe kolagjenozat [12,13].

REZULTATET

Në periudhën kohore Janar 2017 – Dhjetor 2019, janë ekzaminuar 205 fetuse nga 187 shtatzëni (14 shtatzëni gemelare, dy trinjake). Pjesa më e madhe e ekzaminimeve është realizuar në Kliniken e Pediatrisë dhe Poliklinikën "ECHO –SCAN" në Prishtinë. Një pjesë e vogël e ekzaminimeve është kryer në Qendrën Kryesore të Mjekësisë Familjare në Prishtinë. Gjithsej janë realizuar 342 ekokardiografi fetale. Çdo fetus është ekzaminuar 1 - 4 herë (mesatarisht 1.6± 0.6 herë). Ekzaminimi i parë është kryer në mes të javës 14-të dhe 38-të të shtatzënisë (mesatarisht në javët 25.9 ± 9.2).

Të gjitha ekzaminimet fetale ekokardiogafike janë punuar në ekip, pjesë e të cilit ishin: pediatri kardiolog dhe obstetri. Ekzaminimet janë bërë me aparaturën e firmës Acuson ASPEN Advanced, Acuson Sequoia 256, Siemens 300 dhe HP 300 HDL. Janë shfrytëzuar sondat multifrekuenciale me Doppler dhe Color Doppler, me

frekuenca prej 7.5, 5, dhe 3.5 Mhz.Të gjitha ekzaminimet janë regjistruar në DICOM, hard disk ose video shirita SVHS me qëllim rivlerësimin e rasteve të paqarta në një kohë të dytë.

Gjatë punës janë aplikuar të gjitha metodat ekografike: Metoda dydimensionale, metoda M-mode (monodimensionale), metoda Doppler dhe Color Doppler.

Gjetjet fetale ekokardiografike janë krahasuar dhe vërtetuar me gjetjet postnatale ekokardiografike. Analizat anatomopatologjike dhe ato histopatologjike janë punuar sipas standardeve ndërkombëtare (CESDI).

PËRPUNIMI STATISTIKOR

Vlerësimi i metodës së ekokardiografisë fetale në diagnostikimin prenatal të sëmundjeve të zemrës është bërë përmes katër parametrave statistikorë: sensitivitetit, specifitetit si dhe vlerave pozitive dhe atyre negative të parashikimit (vlerave parashikuese).

Sensitiviteti i metodës përkufizohet si probabilitet që gjetja të jetë pozitive në qoftë se e ekzaminuara ka keqformim, në këtë rast si aftësi e metodës së ekokardiografisë fetale ta njohë zemrën e dëmtuar.

Specifiteti paraqet probabilitetin se gjetja do të jetë negative nëse i ekzaminuari nuk ka keqformim të zemrës, gjegjësisht aftësinë e metodës për ta njohur zemrën e shëndoshë.

Vlera parashikuese pozitive paraqet probabilitetin se pacienti ka sëmundje në bazë të testit pozitiv.

Vlera parashikuese negative është probabiliteti se pacienti nuk ka sëmundje në bazë të testit negativ.

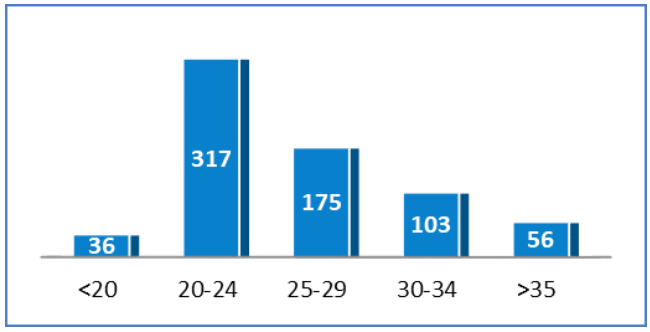
Përpunimi i të dhënave është bërë me paketën statistikore InStat 3. Të dhënat e përftuara janë prezantuar përmes tabelave dhe grafikëve. Prej parametrave statistikorë janë llogaritur indeksi i strukturës, mesatarja aritmetike dhe devijimi standard. Gjithashtu është llogaritur edhe sensitiviteti, specificiteti, vlera prediktive pozitive dhe vlera prediktive negative. Testimi i të dhënave kualitative është bërë me X2-test. Verifikimi i testeve është bërë me shkallën e besueshmërisë 99.7 % ($P < 0.01$) dhe me besueshmëri prej 95 % ($P < 0.05$).

POPULLATA E EKZAMINUAR DHE DISKUTIMI

Në ekzaminim janë përfshirë 205 fetuse nga 187 shtatzani, (14 shtatzëni kanë qënë binjake, dy trinjake). Gjithsej janë bërë 342 ekzaminime të ekokardiografisë fetale. Të gjitha ekzaminimet janë bërë në mënyrë ekipore nga ana e pediatrit kardiolog dhe obstetrit-perinatolog. Çdo fetus është ekzaminuar 1- 4 herë (mesatarisht 1.6 ± 0.6 herë). Ekzaminimi i parë është bërë midis javëve 14-të dhe 38-të të shtatzënisë (mesatarisht në 25.9 ± 9.2 JG).

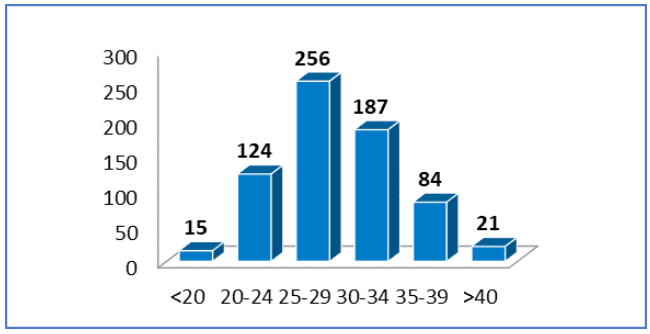
Gjatë studimit kemi vërejtur se ekzistojnë disa dallime të rëndësishme në moshën e shtatzënisë kur është kryer për herë të parë ekzaminimi ekokardiografik fetal, indikacionet për kryerjen e këtij ekzaminimi dhe patologjitë e konstatuara. Për këtë arsye, disa parametra të rëndësishëm i kemi paraqitur njëherë së bashku dhe pastaj kemi bërë krahasimin e gjetjeve midis dy grupeve, për të evidentuar ndryshimet që kanë rëndësi në studim.

Shtatzënat i kemi ndarë në intervale 5-javore varësisht moshës së shtatzënisë kur kanë kryer ekzaminimin ekokardiografik fetal, duke filluar prej javës së 15-të gestacionale deri në javën e 38-të gestacionale. Mosha e grave shtatzëna të ekzaminuara varion midis 16 - 47 vjeç (mesatarisht 28+-5.2 vjeç). Shpërndarja e fetuseve të ekzaminuar sipas moshës është treguar në Grafikun 1.

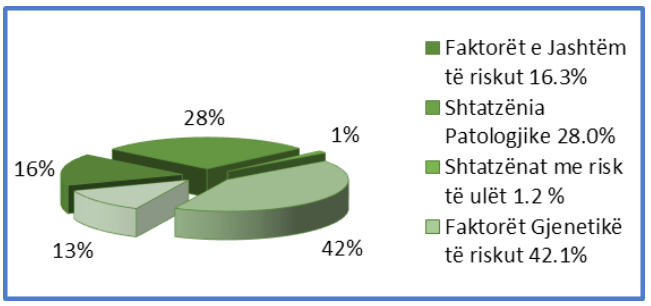


Grafiku 1. Numri i ekzaminimeve (EEF) sipas moshës së shtatzënisë

Shpërndarja sipas moshës është treguar në Grafikun 2. kurse shpërndarja e grupeve të ekzaminuara sipas faktorëve të riskut është treguar në Grafikun 3.



Grafiku 2. Shpërndarja e EEF sipas moshës grave shtatzëna të ekzaminuara.



Grafiku 3. Indikacionet për ekokardiografi fetale

Ndarja e shtatzënave të ekzaminuara sipas indikacioneve

Indikacionet për ekzaminimin ekokardiografik fetal në 187 gratë shtatzëna janë treguar në tabelën 5. Në përgjithësi, numri më i madh i shtatzënave të rekomanduara për ekzaminimin ekokardiografik fetal i korrespondon anamnezës familjare për KLZ.

Gjatë shtatzënisë fetuset janë ekzaminuar 1 deri 4 herë, mesatarisht 1.6 (SD ± 0.6 herë)dhe janë realizuar gjithsej 685ekzaminime prej të cilave 30 ose 4.4% para javës së 20 të shtatzënisë, 328 ose 47.9% prej 20-24 javë, 168 ose 24.5% prej 25-29 javë, 104 ose 15.2% prej 30-34 javë dhe 55 ose 8.0% prej 35 e më shumë javë. Mesatarja e moshës gestacionale kur janë ekzaminuar shtatzënat është 25.9 javë (DS ± 9.2 javë shtatzënie).

Sipas moshës së shtatzënave, numri më i madh i rasteve kanë qenë i moshës 25-29 vj (27.7%), pastaj i moshës 40+ (22.9%) dhe 35-39 vj (20.7%), kurse numri më i vogël i rasteve ka qenë i moshës <20 vj (4.8%). Ndryshimi në shpërndarjen e shtatzënave sipas grupmoshave dhe qendrave ka qenë statistikisht i rëndësishëm (p<0.001).

Gjatë screeningut ekokardiografik për diagnostikimin e KLZ kemi konstatuar gjetje jonormale në 21.3% të rasteve. Shpeshtësia e gjetjeve abnormale gjatë screeningut ka qenë e ngjashme sipas qendrave diagnostikuese (p=0.465) dhe në korelim me gjetjet e qendarve tjera. Mosha mesatare e shtatzënave te fetuset me KLZ ka qenë 31.4+/-6.1 vjeç.

INDIKIMET PËR EF	NUMRI	%
Anamneza familiare për KLZ:	289	42.1
Tek fëmija i mëparshëm	234	34.1
Tek njëri prind	43	6.3
Te kushërirët e shtatzënës	12	1.7
Faktorët amtarë të riskut	85	12.4
Diabet mellitus	66	9.6
Kolagjenozat (SLE, Sn. Sjogren)	8	1.2
Abortet habituale	9	1.3
Mosha amtare mbi 35 vjet	2	0.3
Faktorët e jashtëm të riskut	112	16.3
Infeksionet në tremujorin e parë	79	11.5
Marrja e barnave	26	3.8
Ekspozimi ndaj rrezatimit	7	1.0
Shtatzënia aktuale patologjike	193	28.0
Hidropsi fetal	6	0.9
Polihidroamnion	44	6.4
Oligoamnion	2	0.3
IUGR	18	2.6
Keqformimet ekstrakardiale të frytit	18	2.6
Aberacionet kromozomale	3	0.4
Infeksionet e frytit	7	1.0
Alfa fetoproteina e ulur	3	0.4
Gjestacionet multiple	5	0.7
Rekomanduar nga gjinekologu për:		
- Çrregullimeve të ritmit të frytit	33	4.8
- Dyshimit në KLZ (prerja katërhapësinore patologjike)	54	7.9
Screening-u rutinor	8	1.2

Tabela 1. Shpërndarja e grave shtatzëna të ekzaminuara sipas indikacioneve

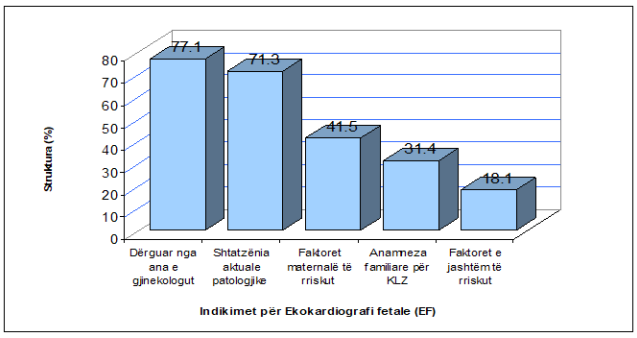
Indikacioni më i shpeshtë për kryerjen e EF në numrin e përgjithshëm të rasteve ka qenë me rekomandim të gjinekologut (77.1%), dhe ate për shkak të dyshimit për KLZ (66%), çrregullimit të ritmit të zemrës së frytit (11.2%) dhe screeningut rutinor (9.6%).

Si indikim i dytë kanë qenë shtatzanitë aktuale patologjike (71.3%), nga të cilat më së shpeshti kanë qenë IUGR (14.9%) dhe polihidroamnioni (12.2%). Faktorët maternalë të rriskut kanë paraqitur grupin e tretë të indikimeve për EF sipas shpeshtësisë (41.5%), prej të cilave mosha e shtatzënave mbi 35 vjeç ka qenë indikacioni më i shpeshtë për ekzaminim (24.5%) dhe DM (9.6%). Anamneza familjare pozitive për KLZ ka qenë grupi i katërt i indikimeve për EF sipas shpeshtësisë (31.4%), kurse faktorët e jashtëm të rriskut kanë qenë indikacioni më i rrallë për EF (18.1%).

Te grupi i fetuseve me KLZ indikacioni më i shpeshtë për EF ka qenë dyshimi në KLZ (52.5%), faktorët maternalë të rriskut (22.5%) dhe anamneza familjare pozitive (12.5%), kurse indikacioni më i rrallë ka qenë shtatzania aktuale patologjike (5.0%).

Sipas qendrave indikacioni për EF ka qenë shumë i ndryshëm. Në qendrën e Xhenovës në gjysmën e rasteve

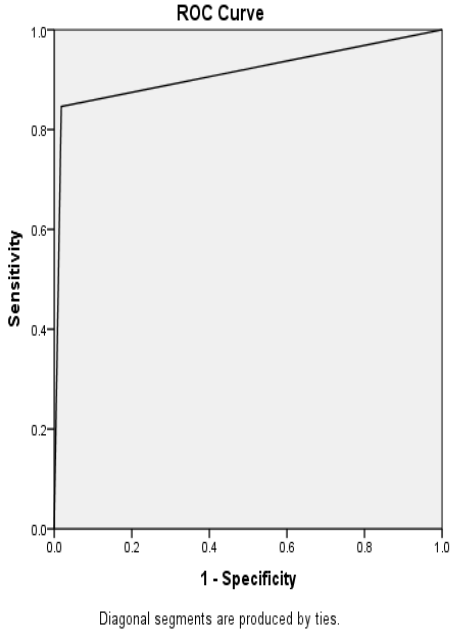
si indikacioni për EF kanë qenë faktorët maternalë të rriskut, kurse në 41.7% dyshimet për KLZ. (Grafiku 4).



Grafiku 4. Indikimet për EF sipas grupeve të indikimeve

Indikacioni më i shpeshtë për EF ka qenë dyshimi për KLZ (57.1%) dhe anamneza familjare pozitive (14.3%). Nga tri raste (10.7%) si indikim kanë pasur faktorët amtarë, përkatësisht çrregullimet e ritmit të zemrës së frytit.

Ekokardiografia fetale, si metodë për diagnostikimin e hershëm të KLZ te fetusit, është treguar metodë me efikasitet të lartë diagnostikues, përkatësisht me sensitivitet 90% dhe specificitet 97.3%, me vlerë parashikuese pozitive 90%, përkatësisht vlerë parashikuese negative 97.3%. (Grafiku 5).



Grafiku 5. ROC lakorja e EEF për diagnostikimin e KLZ në Prishtinë

Area under the Curve = 0.914

Në këtë aspekt, së pari duhet të kemi parasysh se diagnostikimi antenatal i KLZ dhe përvojat në këtë fushë janë ende të reja dhe shumë përgjigje mbeten të hapura dhe janë burim diskutimesh të gjëra. Qëndrimet lidhur me shtatzënitë e diagnostikuara me KLZ në fillim kanë qenë të ngjashme me qëndrimet ndaj shtatzënive me keqformime të organeve apo sistemeve të tjera dhe këto qëndrime mund të quhen qëndrime negative eugjenike [15,16].

Mirëpo, qëllimi i diagnostikimit antenatal në përgjithësi dhe specifikisht ai i diagnostikmit antenatal të KLZ nuk është seleksionimi negativ i fëmijëve me keqformime por ka për synim që në mënyrë shkencore dhe objektive të vlerësohet prognoza individuale e çdo shtatzënie si dhe opsioni për ti mundësuar çdo fëmije me KLZ mbijetesën dhe lindjen me pasoja sa më të vogla [17,18].

Por, një tendencë e tillë na vendos para një pyetje thelbësore: sa e besueshme është ekokardiografia fetale në diagnostikimin antenatal të KLZ?

Përgjigjën në këtë pyetje do ta kërkojmë nga disa tregues objektiv të fituar nga përvoja botërore në këtë fushë si dhe nga përvoja dhe rezultatet tona të prezantuara në këtë punim.

Përvojat e deritanishme në botë por edhe te ne janë tregues i besueshëm dhe të majftueshme pë të treguar se diagnostikimi antenatal i sëmundjeve të lindura të zemrës është një realitet dhe përvojë e mirë. Por, përkundër përvojës së mjaftueshme në botë dhe te ne si dhe përparimeve të cilat janë bërë në zhvillimin e teknologjisë ekografike (aplikimi i Doppler-it, ekokardiografisë 3D dhe 4D) sërish duhet të jemi mjaft të kujdesshëm dhe të vetëdijshëm për mundësinë e gabimeve dhe rezultateve fals pozitive apo fals negative. Nga përvoja e përgjithshme dihet se një metodë diagnostike mund të vlerësohet në aspektin shkencor vetëm në bazë të rezultateve dhe parametrave statistikorë, konkretisht përmes krahasimit të rezultateve antenatale me gjetjet postnatale (rezultateve anatomo-patologjike, ekokardiografike, intraoperative, etj) për të cilat do të diskutojmë në vazhdim.

Vlera e lartë parashikuese negative (te shumica e autorëve kjo vlerë varion midis 98 deri 99 %) si dhe vlera e lartë e specificitetit të kësaj metode (rreth 99 %) janë tregues i mirë se ekokardiografia fetale mundëson përjashtimin e pranisë së KLZ.

Vlera realtivisht e lartë parashikuese pozitive (prej 81 deri 98 %) si dhe vlera e lartë e sensitivitetit të ekokardiografisë fetale (midis 70 dhe 93 %) tregon se në shumicën e rasteve KLZ mund të diagnostikohen në moshën antenatale.

PËRFUNDIME DHE KONKLUZIONE

Duke bërë një përmbledhje të rezultateve tona në këtë fushë dhe në kushtet dhe mundësitë aktuale në Kosovë, ku shërbimi i ekokardiografisë fetale është në zhvillim e sipër kurse shërbimi i kardiokirurgjisë pediatrike nuk ekziston, mund të konkludojmë se përgjigjia në pyetjen kryesore të sipërpërmendur mund të shtjellohet në disa pika:

Ekokardiografia fetale është një metodë e realizueshme diagnostike që synon diagnostikimin antenatal të KLZ

Kjo metodë mundëson diagnostikimin e shumicës së KLZ dhe çrregullimeve të ritmit të zemrës në periudhën antenatale

Nuk është aspak më i rëndësishëm fakti se ekokardiografia fetale mundëson eliminimin e dyshimit në KLZ

Mundësia e diagnostikimit fals pozitiv dhe fals negativ kërkon kujdes dhe përvojë në konkludimin dhe konfirmimin e llojit dhe natyrës së KLZ;

Në shumicën e rasteve të diagnostikimit fals negativ bëhet fjalë për KLZ me prognozë të mirë postnatale, qoftë pas intervenimit kardiokirurgjik/kardiologjik, qoftë me mbylljen spontane.

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Profesional paper

EDUCATION OF FAMILY DOCTORS AND ADHERENCE TO GUIDELINES ON ANTIBIOTIC PRESCRIBING FOR ACUTE RESPIRATORY INFECTIONS

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ABSTRACT

Acute respiratory infections are one of the most common reasons for visiting family doctors. An increased prescribing of antibiotics is a global health problem. Implementation of guidelines in practice could reduce antibiotic prescribing.

Objectives: to determine the impact of one day targeted education of family doctors on adherence to guidelines for acute respiratory infections and antibiotic prescribing.

Methods: The study is a part of the National Project for antibiotic prescribing for acute respiratory infections. The survey was done as an analytical case control study implemented in November 2016 at the Primary Health Care in Republic of North Macedonia. In the research group participation took 95 doctors divided in two groups. Investigated group of 49 doctors received previous one day education for acute respiratory infections according to the national guidelines. The control group included 46 doctors, without education. A research questionnaire was fulfilled. The results obtained are analyzed by using standardized analytical methods.

Results: An analysis of a sample of 8259 patients found that the antibiotic prescribing rate in the investigated group was 60.5% and 59.7% in the control group.We found no significant differences between the groups (p = 0.4644). The most prescribed AB in the both group was Amoxicillin + clavulonic acid.

Conclusion: We concluded that the short targeted education of family doctors did not have a significant influence on increasing adherence to guidelines.

Keywords: antibiotics, respiratory infections, education, guidelines

INTRODUCTION

Acute respiratory infections (ARIs) are one of the most common reasons for visiting family doctors.(1) The increased and unnecessary prescription of antibiotics for ARIs leads to significant health consequences of entire population.(2) The process of antibiotic prescribing is a very complex, with a lot of predictive factors and involving doctors, patients and health policy.(3) Crucial for prescribing is the proper communication and consultation skills of the doctors.(4) Continuous medical education (CME), knowledge and practicing Evidence Based Medicine guidelines, could contribute to the rational antibiotic prescribing.(5) Consequences of unnecessary prescription of antibiotics for ARIs are the appearance of increased bacterial resistance, complications, prolonged hospitalization, adverse side effects, medication, overprotection of doctors, stimulation of misconceptions and prejudices in patients, motivation of patients for multiple visits to the doctor and unnecessary discharge of health insurance funds. (6,7) Eighty percent (80%) of the prescribed antibiotics are prescribed at primary care level. The reasons for this excessive prescribing of antibiotics are numerous. (3, 8)

The data show that in the treatment of ARIs there is an excessive use of antibiotics, which are not in accordance with the diagnosis and national guidelines. (7) There is increased tendency for the use of macrolide antibiotics. (9) For the need to reduce the use of antibiotics a number

of international research and educational activities have been carried out using various educational strategies and measurement of the results. (1,9,10) Emphasizing the need for more rigorous compliance with the guidelines and unification of doctors in the treatment of ARIs will reduce the prescription rate of antibiotics. (5,11) Greatest success in reducing the prescription of antibiotics has been achieved by the Nordic countries. (9) The World Health Organization has as a priority the rational prescribing of antibiotics in order to influence on bacterial resistance.(12) Family doctors have a key role in the increased prescription of antibiotics. (3,10) The integrated packages of interventions implemented have proved to be the most effective in reducing the prescription of antibiotics.(14,15) Antibiotic prescribing is still considered to be a room for improvement.(13) Despite the implementation of a number of different educational interventions, it has been established that the effect is different and insufficient.

METHODS

Design of the study

The study was a part of the National Project for antibiotic prescribing for ARIs. The survey was conducted by Center of family medicine as an analytical case control study that was implemented in November 2016 in seven regions of Republic of North Macedonia. A total of 95 family doctors (examined and control group) were included in the research. The selection was carried out in seven regions of the country by a simple random selection method in accordance with previously defined inclusion and exclusion criteria. Each of the doctors had an obligation to fulfill out a research questionnaire for all patients with ARIs who visited their primary care clinics in November. The total number of patients with ARIs covered by the study was 8259 patients.

Inclusion criteria: work in primary health care, to ordinate in one of the seven selected regions, minimum of 3 years of work experience, concluded contract with Health Insurance Fund, irrespective of gender, age, religion, social status and other socio-demographic characteristics, readiness and willingness to participate in the study.

Exclusion criteria: work in secondary or tertiary health care, organizing outside the seven selected regions, under 3 years of work experience, no contract has been concluded with Health insurance fund, absence of readiness and willingness to participate in the study.

Characteristics of the sample

Examined group - This group included a total of 49 family physicians that had been trained in the seven selected regions for the research. In October 2016, for these doctors was conducted one-day education on the diagnosis and treatment of ARIs, with a special emphasis on the need for proper prescribing and prescribing antibiotics in accordance with national guidelines. The education was conducted in the form of educational lectures for the most common ARIs, diagnostic criteria and treatment in accordance with national guidelines. Work was carried out in small groups with scenarios and clinical skills: training proper use and interpretation of Rapid Antigen Strep Test (RAST), Rapid C-reactive protein tests (CRP).

Control group - this group includes a total of 46 doctors. Doctors from this group were not received additional targeted education. Each of the doctors in the two groups, during November 2016, had an obligation to fullfill out a research questionnaire for all of the patients with ARIs who visited his office in November 2016.

Research questionnaire

Two questionnaires were used in the research study

1. First questionnaire - Each doctor, before completing this questionnaire, received a form for information and a consent form for participation in the research. This questionnaire refers to the socio-demographic characteristics of the doctor as well as the specifics of his/her practice. Each doctor participating in the research had provided its own identification number to ensure the anonymity of the doctors participating in the study.

2. Second questionnaire - This questionnaire is a newly designed questionnaire for the needs of the project and is composed of several parts.The questionnaire fullfills the doctors with a prior consent from the patients.

STATISTICAL ANALISYS

The data obtained from the research were processed in appropriate statistical programs (Statistics for Windows 7.0 and SPSS version 14. A significance level of $p < 0.05$ was used to determine statistical significance.

RESULTS AND DISCUSSION

In the whole sample of 95 family doctors, 49(51.58%) were

included in examined group, while 46(48.42%) in control group. Statistically we did not find statistical significancy between both groups of doctors, p>0.05 (Difference test: Difference 3.16% [(-10.86-17.01) CI 95%]; Chi-square = 0.189; df= 1 p= 0.664).

The total number of 95 doctors was analyzed according their specialization: 52(54.74%) were family specialist or pediatricians, while 43(45.26%) were general practitioners (non-specialists). The total number of patients with ARIs, treated by doctors-specialists (family specialist and pediatrician) is 4684(56.71%), while the number of patients treated by general practitioners is 3575(43.29%). The percentage of the patients with ARIs treated by specialists and those treated by non-specialists in the entire sample is statistically significant for p <0.05 (Difference test: Difference 13.42% [(11.91-14.93) CI 95%]; Chi-square =297.46; df= 1 p= 0.0001) in favor of significantly greater number of patients treated by doctors-specialists which indicate that the long-term education of doctors significantly affects the quality of work and increased number of patients.

Socio-demographic characteristics of the patients in the sample

The survey covered a sample of 8259 patients with ARIs. This part of the survey shows the sample analysis according to certain demographic characteristics in both groups. The analysis of the those parameters was made in relation to the treatment of a doctors in both groups.

Table1 Analysis of socio-demographic characteristics of the sample

	Examination group	Control group	Total (examined/ control group)	Statistics	P<0.05	
Gender	m=2119/f=2269 53.96%/ 54.11%	m=1808/f=1924 46.04%/45/89%	3732/4388 54.04%/45/96%	Pearson Chi-square=0,1942 df=1	P=0.8892	
Age	21,3±22,3 y.50%>11 y.	23,2±23,2 y.50%>12 y.	22,2±22,7 y. 50% > 11 y.	Mann-Whitney U Test: Z=-3,027 Pearson Chi-square=26,233; df=5	p=0,0025* p=0,00008*	
Kinder garden visit	Yes 651(37.39%) No 655(44.23%)	Yes 1090(62.61%) No 826(55.77%)	1306 (40.53)% 1916 (59.47%)	Pearson Chi-square=15,508, df=1	p=0,00008*	
Education of the mothers	Without 169 (6.21%) Basic 623 (22.54%) Median 1388 (51.03%) High 457 (21.58%)	Without 58 (2.74%) Basic 426 (20.11%) Median 1177 (55.57%) High 457 (21.58%)	2720/2118 56.22%/43.78%	Pearson Chi-square=39,585, df=3,	p=0,00001*	
Working status	Students 65 (3.89%) Employed839 (50.24%) Unemployed 457 (27.37%) Retired=309 (18.50%)	Students48 (3%) Employed751 (46.88%) Unemployed 449(28.03%) Retired 354 (22.10%)	113(3.45%) 1590 (48.59%) 906 (27.69%) 663 (20.26%)	Pearson Chi-square=9,1436, df=3	p=0,0274*	
Days of the week	Monday 1241(27.93%) Tuesday 835(18.79%) Wednesday 841 (18.93%) Thursday 714 (16.07%) Friday 752 (16.93%) Saturday 60 (1.35)	Monday 1077 (28.41%) Tuesday 695 (18.33%) Wednesday 619 (16.33%) Thursday 608 (16.04%) Friday 696 (18.36%) Saturday 96 (2.53%	4443 (53.96%)/3791 (46.04%)	Pearson Chi-square=25,675, df=5	p=0,0001*	
Kind of visit	First visit 3781 (85.27%) Control 653 (14.73%)	First visit 3163 (84.26%) Control 591 (15.74%)	4434(54.15% /3754(45.85%)	Pearson Chi-square=1,6289, df=1	p=0,2018	
Comorbidities	Asthma 128(2.87%) COPD 164(3.68%) Diabetes 136(3.05%) Heart failure 96(2.15%) Cirrhosis 5(0.11%) Others 255(6.61%)	Asthma 72(1.89$) COPD 152(4%) Diabetes 111(2.92%) Heart failu 118(3.11%) Cirrhosis 2(0.05%) Others 251 (5.72)	1252/15.2%	Difference test: Difference 6,71% [(2,86-10,53) CI 95%]; Chi-square=11,651; df=1 (between COPD/diabetes)	p=0,0006*	
Days with symptoms	n 3902/3.61 days min. 1;max.31	n 3600/4.15 days min.1; max.31	n7502/3.87 days min.1;max.31	Std. Deviation: 2.63/3.36 Mann-Whitney U Test: Z=6,114;	p=0,00001*	

Analysis of the sample according to gender and treatment of doctors from examined and control group indicate no statistically significant association between the sex and the groups of patients. In the whole sample there is predominance of the female patients. This could stimulate thinking that females have a traditionally increased responsibility for the personal and family's health. A meta-analysis and systematic review was made where the difference between the sex and the use of antibiotics was determined, in addition to the female gender predominance. In a sample of 4.57 million patients, 67% of women received antibiotics more than men, and excluding those antibiotics used for urinary infections, for ARIs accounts 43%. No explanation can be given for this difference between the sexes. It is assumed, there is a difference in the habits and behavior of women for more frequent visits to the family doctor than men and even 80% of healthy women more often visited a doctor than men.(16,18)

The difference test between the two groups according to the average age of the patients shows a significantly higher number of patients from younger age groups in the examined group and existence of an elderly category of subjects in the control group.

The results show that the most prevalent age group in the whole sample is the group of 0-3 years. It points to the fact that infants and young children are the most affected group with ARIs. Children are the most frequent visitors to family doctors and pediatricians and use most antibiotics for ARIs. The established significant statistical difference between the groups in the number of patients from the younger age groups, in addition to the examined group, could be the one of the reasons for increased use of antibiotics. (17)

Pre-school children, were analyzed regarding the visit to kinder garden. There is a statistically significant association between the group (examination / control) of which the patient belongs and a visit to kinder garden in addition to significantly more children attending a kinder garden in the control group. Some studies shows different percentage of antibiotic prescribing in children who visit kinder garden. (2)

All children's patients (0-18 years old) were analyzed in terms of educational level of the mothers. A significant association was established between the mother's education of a child patient and the patient's group in addition to a significantly higher number of mothers without education in the examined group. (18)

Patients older than 18 years are analyzed in terms of their working status. A significant association was established between the working status and the patient's group in addition to an increased number of patients with working status in the examined group.This could have an impact on the antibiotic prescribing rate in the examined group. This phenomenon is explained by the fact that the working population for maintaining work efficiency and avoiding absences from work, more often visit the doctor because of the ARIs and use antibiotics greater than the rest of the population.

The results of the analysis of the entire sample of patients and the days of the week they visited the doctor show the highest number of visits on Monday, followed by Tuesday and Friday. Monday is the day after the weekend and patients due to symptoms of illness they felt at the weekend are visiting a doctor. Friday is the day before the weekend which is also critical for patients. Compared to the results obtained from research in Germany, a higher AB prescribing rate was found on Friday by 23.3% higher than other days of the week, although there is a periotic fluctuation in other days of the week. This shows that it is necessary to determine the factors for this phenomenon in order to developing an appropriate strategy to reduce the prescription. (20)

Regarding the percentage distribution of the indicated comorbidities in the sample, it is predominantly COPD and diabetes, followed by heart disease and asthma. The emergence of this significant statistical difference in relation to other comorbidities is expected and corresponds to data in other European countries, due to the increased percentage of cigarette smoking, air pollution and poor life habits.(20)

In the examined and control group dominant symptoms are consequently the sense of disease in 1745 (58.4%) vs 1244 (41.62%) cases and cough in 2435 (54.6%) vs 2389 (62.9%) cases and a runny nose in 1955 (43.84%) vs 1618 (42.6%) cases. The results according the days with the symptoms show shorter duration of the symptoms in the examined group.

The majority of patients in the sample had a temperature of ≤ 380C C which means that the most of the patients had an easy form of fever but because of the easy accessibility to the family doctors, fear of complications, insufficient education and the desire for early antibiotic treatment, patients or parents visit the doctor to early for antibiotic

treatment. Patients have a meaning that early initiation of antibiotic therapy will prevent complications, although most ARIs have viral etiology and the administration of antibiotic does not change the course of the disease. This implicates need of new research connected with patient's unsatisfied needs and education for ARIs. The greatest benefit would be achieved by implementation of system for appointment visits to family doctors. On the other hand it is necessary to make more rigorous interventions for doctors at all levels of health care to increase adherence to guidelines and changes in health policy. (21)

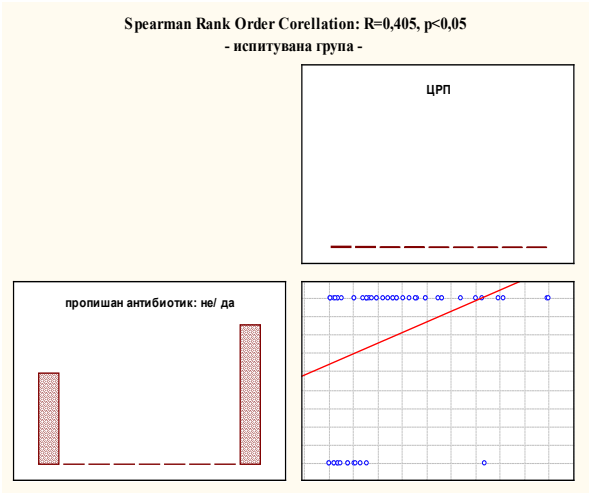
Physical examination findings of tonsils were made by dividing the findings into five groups. Within the entire sample, hyperemic tonsils were found in 4048 (56.77%) of the patients, swollen tonsils in 1556 (22.7%), pus of tonsils in 370 (5.4%), previous tonsillectomy in 93 (1.4 %) and normal finding in 3224 (44.3%) patients. According to these findings only 5.4% of the patients should be treated.

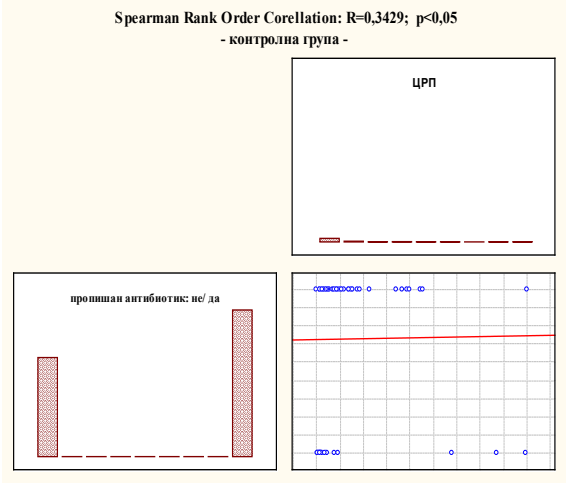
Table2 Analysis of the examined and control group according realization of RAST

	Examination group	Control group	Total (examined/ control group)	Statistics	P<0.05
Entire simple					
RAST	No 3090 (86.99%) Yes 462 (13.01%)	No 2936 (82.66%) Yes 616 (17.34%)	No 6026 (84.83%) Yes 1078 (15.17%) 7104(100%)	Pearson Chi-square=25,936 ; df=1	p=0,000001*
Simple with antibiotics					
	No 1562 (84.52%) Yes 286 (15.48%)	No 1656 (83.05%) Yes 338 (16.95%)	Total No 3218 (83.76%) Total Yes 624 (16.24%)	Pearson Chi-square: 1,533, df=1	p=0,2156

The results from the Table 2 show significant association between the made RAST and the patient's group with a significantly lower number of RAST in the examined group. In a whole sample of patients with a prescribed antibiotic, no significant association was found between the number of RAST and the treatment of a doctor with / without education. The doctors in both groups do not use enough RAST, and if they use it, there is no significant influence in the decision-making process for antibiotic prescribing and have a low adherence to the national guidelines. This partly could be justified because the health insurance fund does not cover financial expenses for the realization of the RAST.

Analysis of CRP testing for low ARIs shows significantly lower number of CRP analyzes in the examined group. The analysis of the interrelation between the levels of the CRP values and the prescribing of antibiotics indicated the existence of a significant linear positive correlation in the examined group, while in the control group established a significant linear positive moderate correlation. A significant difference was found between the two correlations and a more significant correlation was found in the examined group.



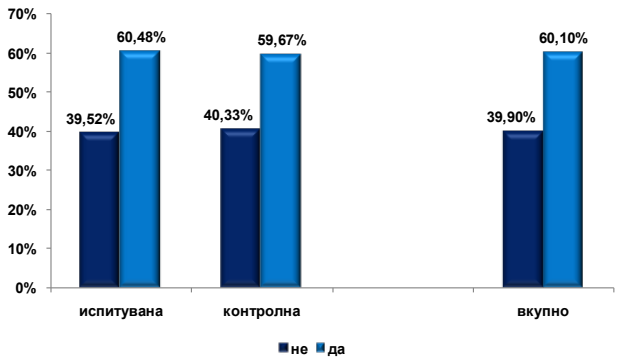


The analysis of the interrelation between the levels of the CRP values and the prescribing of antibiotics between the groups

This could indicate that doctors are aware of the diagnostic value of the rapid CRP test and it,s significance in antibiotic prescribing decision for lower ARIs.(24) The use of the CRP test in the primary care is still limited, because the fast CRP test is expensive and is not paid by insurance health fund.

The most common ICD10 diagnosis was J00-cold (rhinitis, pharyngitis) in 1887 (25.4%) followed by J03-acute tonsillitis represented by 1455 (19.6%), J02-acute pharyngitis in 1178 (15.8%) and J20 -acute bronchitis in 1134 (15.3%). The least common diagnosis in the sample is J05-croup and epiglottitis represented with 5 (0.1%) followed by H60-otitis external 25 (0.3%) and J11-influenza in 38 (0.5%). This shows that 60.8% of patients had mild upper respiratory infections, and the most patients don't require antibiotic therapy, and this indicates absence of adherence to the guidelines.

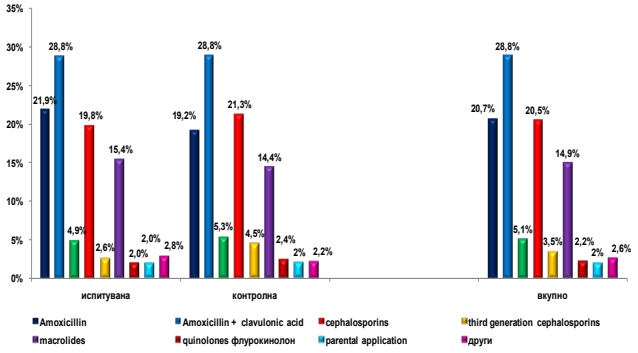
Fig.2 Analysis of the sample by groups and prescribed antibiotics



In the whole sample, an antibiotics were prescribed in a total of 4831 (60.1%) of patients. In the examined and control group, antibiotics were prescribed consequently in 2595 (60.5%) v.s 2236 (59.7%) patients. For p> 0.05, there is no significant association between prescribing antibiotics and the patient' group (p = 0.4644).

Patients in the examined and control group in whom the antibiotics were prescribed were analyzed for the type of antibiotic.

Fig3 Analysis of the simple according the groups and type of prescribed antibiotic



The most common used antibiotic in the whole sample is Amoxicillin + clavulonic acid, followed by Amoxicillin. The least used group of antibiotics in the examined group was fluoroquinolones. For p <0.05, the significant percentage difference between the examined and control group was determined for: a) Amoxicillin (Difference test: Difference 2.67% [(0.37-4.95) CI 95%]; Chi-square = 5.18; df = 1 p = 0.0229) in addition to a significantly greater prescription in examined group; and b) a third generation of cephalosporins (Difference test: Difference 1.89% [(0.85-2.98) CI 95%]; Chi-square = 12.776; df = 1; p = 0.0004) in addition to significantly greater prescribing in control group. The increased use of amoxicillin demonstrates greater adherence to the guidelines by the examined group. These results also indicate lack of adherence to the guidelines in control group.

There was no significant difference between the two groups in terms of prescribing: Amoxicillin + clavulonic acid (p = 0.9635), cephalosporins first and second generation (p = 0.202), Penicilin V (p = 0.571), macrolides (p = 0.327) , quinolones fluoroquinolone p = (0.296), parenteral application (p = 0.843) and other (p = 0.168). The low percentage of prescribing Penicillin V (5.1%) for sore throats indicates the lack of adherence to national guidelines in both groups, in contrast to studies in European countries where this percentage is significantly higher.(25)

The average duration of therapy with antibiotics in the whole sample was 6.4 ± 1.9 days, 50% of patients with duration of therapy longer than 7 days. For p <0.05, there is a significant difference in the mean duration of antibiotic therapy between the two groups, in addition to a significantly longer duration (p = 0.00001) of antibiotic treatment in a control group that also does not correspond with the recommendations of the guidelines.

(26) For p <0.05, there is a significant difference in the average duration of antibiotic therapy between the two groups (Mann-Whitney U Test: Z = -6.867; p = 0.00001) in favor of a significantly longer duration in the control group.

The majority of patients received antibiotic therapy orally. Although the percentage of parenteral application in primary health care is very low but there is a need for further decreasing.(27)

CONCLUSION

We concluded the short-term targeted education of family doctors did not lead to a significant reduction of antibiotic prescribing for ARIs in practice, did not lead to significant changes in the performance of family doctors in choosing proper antibiotic for different ARIs. The use of RAST and the CRP test in Primary Care are limited. RAST is not in association with the number of prescribed antibiotics for upper ARIs. The most commonly used antibiotic in both groups is amoxicillin + clavulonic acid. Prescription of Penicillin for upper ARIs is extremely low. The examined group prescribes a higher percentage of amoxicillin and control group use significantly third generation of cephalosporins. Regarding the treatment with antibiotics for ARIs in both groups, we found a low adherence to the national guidelines. A lot of factors can influence on decision making of doctors. This suggests that maybe more complex, longer-lasting and combined educational strategies for family doctors, implementing patient education programs, and health policy changes would significantly change the antibiotic prescribing habits of family doctors for ARIs.

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Profesional paper

КЛИНИЧКИ КАРАКТЕРИСТИКИ И ХИСТОМОРФОЛОШКИ ОДЛИКИ НА АНГИОГЕНЕЗАТА КАЈ РЕЦИДИВАНТНИТЕ ПТЕРИГИУМИ

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АБСТРАКТ

Рецидивантен птеригиум е формација на фиброваскуларно крилце, кое се јавува на местото на претходно извршената екцизија на птеригиум, чија глава го поминува лимбусот на роговицата.

Цел: иследување на клиничките карактеристики и хистоморфолошките одлики на ангиогенезата кај рецидивантните птеригиуми.

Материјал и метод: иследувани се 30 рецидивантни птеригиуми кои се јавиле по екцизија на примарен птеригиум со проста екцизија на птеригиум или со екцизија и слободна оголена склера или со модифицирана слободна конјунктивална автотрансплантација на конјунктива со графт од горната булбарна конјунктива

Рецидивантни птеригиуми се хируршки отстранети со методата на екцизија на птеригиум со слободна автотрансплантација на конјунктива со графт од долно темпоралната булбарна конјунктива.

Пациентите беа испитувани предоперативно со Haag-Streit 900 шпалт ламба и пост оперативно по првиот, третиот, шестиот, деветтиот, дванаесеттиот месеци, се до 36-тиот месец во зависност од времето на изведената хируршка екцизија. Рецидивантните птеригиум беа документирани и фотографирани со Red Cam.

Хируршки отстранетите рецидивантни птеригиуми се хистопатолошки иследувани во однос на нивната ангиогенеаза и клинички карактеристики, големина, прогресија , рецидиви, Фуксови дамки и Штокерова линија.

Резултати: Постоперативни рецидиви се јавија кај 3 пациенти (10%). Должината на повтореният рецидивантен птеригиуми изнесуваше повеќе од 3 мм (3,89 +-1,02 SD) и истата ја надминуваше зоната на претходно ексцидираниот рецидивантен птеригиум. Средно време на растење на рецидивантните птеригиуми изнесуваше 6,5 месеци. Брзо растечки рецидивантни птеригиуми, почесто беа забележани кај помлади мажи и кај работници кои работат на отворено, незаштитени од УВ зрачење и прашина. Фуксови дамки беа забележани кај 73% од рецидивантните птеригиуми, а Штокерова линија кај 60% . Нежната капиларна мрежа на мултипни крвни садови со дискретно изразена фибриноидна промена во едематозната строма се забележа кај бавно растечките стационирани рецидивантни птеригиуми, додека комплексно богато разгранување на развиените капилари со поголем лумен е знак на прогресивни рецидивантни птеригуми

Заклучок: Рецидивантните птеригиуми се брзо растечки птеригиуми, со богато разгранета мрежа на крвни садови со голем лумен кои допринесуваат за брзо достигнување на големината на претходно ексцидираниот птеригиум кај помлади активни пациенти поради што повторно се нарушува видната острина и предизвикуваат естетски промени.

Клучни зборови: рецидивантен птеригиум, птеригиум, клиничка слика на птеригиум, ангиогенеза на птеригиум,лекување на птеригиум

ВОВЕД

Рецидивантен птеригиум е формација на фиброваскуларно ткиво во вид на крилце, кое се јавува на местото на претходно извршената екцизија на птеригиум, чиј врв или глава го поминува лимбусот на роговицата. Патогенезата на појавата на птеригиумот , неговото напредување или стагнирање или пак постоперативно повторување се уште потполно не се разоткриени (1,2). Честотата на рецидивите кои се јавуваат по отстранувањето на примарните или рецидивантните птеригиуми е различна кај различни медицински иследувања (3,4,5) и пред се зависат од бројни фактори како што е видот на изведената хируршка метода (3,4,6,7) возраста на пациентите, професијата, изложеноста на УВ зрачење (1,2,8), квалитетот и квантитетот на солзниот филм (9), клиничките карактеристики на птеригиумот неговата големина и прогресивност, фактори на ангиогенезата (10), улогата на лимбалните стем клетки (11), имунолошката состојба на предниот сегмент на окото и други фактори и теории (12).

Цел на иследувањето беа клиничките и хистоморфолошки карактеристики на ангиогенезата кај рецидивантните птеригиуми.

Матерјал и метод: иследувани се 30 рецидивантни птеригиуми кои се јавиле по хируршка екцизија на примарен птеригиум со едноставна екцизија на птеригиум или со екцизија и слободна оголена склера или со модифицирана слободна автотрансплантација на конјунктива со графт од горната булбарна конјунктива. Рецидивантните птеригиуми се хируршки отстранети со методата на екцизија на птеригиум со слободна конјунктивална автотрансплантација со графт од долната булбарна конјунктива.

Пациентите се испитувани пред оперативно со Haag-Streit 900 шпалт ламба и пост оперативно по првиот, третиот, шестиот, деветиот и дванаесетиот месец, а потоа секој 6-ти месец се до 36-от месец во зависност од времето на хируршката екцизија на птеригиумите. Рецидивантните птеригиум се документирани и фотографирани со Red Cam.

Иследуваните рецидивантни птеригиуми беа класифицирани според дефиницијата на Sebon и Hirst (13): формација од фиброваскуларно ткиво во вид на крилце, кое се јавува на местото на претходно извршената екцизија на птеригиум, чиј врв или глава го поминува лимбусот и се проширува на корнеата, за разлика од простата васкуларизација на стромата на роговицата.

Ткивните примероци , добиени по хируршката екцизија, беа фиксирани во 10% неутрален, пуфериран формалин и во првите 24 до 72 часа беа транспортирани на Институтот за патологија при Медицинскиот факултет УКИМ во Скопје за понатамошно испитувања. За хистопатолошка анализа ткивните примероци беа рутински обработени, вкалапени во парафин, а 5 микронските пресеци беа боени со стандардното Hema toxylin-Eosin боење. За имунохистохемиско испитување ткивните пресеци беа поставени на Poly-L-Lysine-ски стакла кои обезбедуваат зголемена адхерентност на ткивата и беше користена Avidin Biotin (ABC I LSAB) техника. За визуелизација на ангиогенезата користено е антителото CD34 (DAKO 2:98).

Хистоморфолошки иследувани се и 10 примероци на здрава булбарна конјунктива кај пациенти без птеригиум како контролна група за хистоморфолошките иследувања на рецидивантните птеригиуми

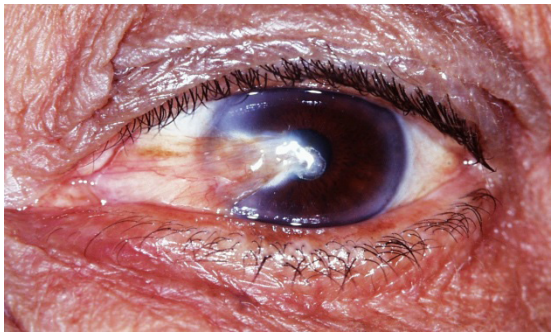
РЕЗУЛТАТИ

Во нашето иследување, рецидивантните птеригиуми најчесто беа со должина од 3 мм и повеќе (3,89 +-1,02 SD) и ја надминуваа зоната на претходно ексцидираниот рецидиватен птеригиум. Кај групата од 30 рецидивантни птеригиуми каде беше изведена хируршката метода на екцизија на птеригиум со слободна автотрансплантација на конјунктива со графт од долно темпорална булбарна конјунктива, постоперативно се добија 3 симптоматски брзо растечки рецидиви (10%).

Средно време на следење на постоперативните рецидиви во просек е 19,80 месеци со SD 5,64. Времето на рецидивирање во групата на повторно јавените рецидивантни птеригиуми изнасува 6,0+-3,0 месеци. Односно рецидивите се забележани на контролните прегледи во 3 , 6 и 9 месец. Појавата на рецидивите беше почеста кај машкиот пол.

При предоперативните и постоперативни иследувања забележани се каратеристичните знаци на прогресија на рецидивантниот птеригиум, како што се Fuchs-ови дамки и Штокеровата линија (сл.1). Пред богато васкуларизираната дупликатура со проминентна месеста глава, се забележуваат ситни, белузлави заматувања во ниво на Bowman-ова мембрана, Fuchs-ови дамки. Фуксовите дамки беа присатни кај 22

пациенти или 73,3 %. Штокерова линија беше присатна кај 18 пациенти со рецидивантен птеригиум или 60 %.



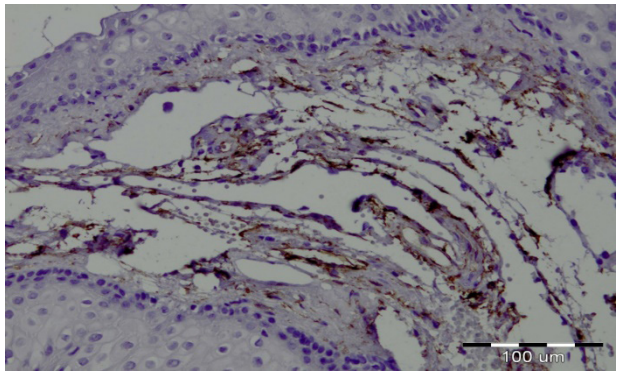
Слика 1. Прогресивен рецидивантен птеригиум чиј врв ја препокрива пупиларната зона. На работ на апексот јасно назначена Stoker-ова линија и Fuchs-ови дамки.

Хистоморфолошки, птеригиумите кои беа анализирани, се опишани и дефинирани како фиброваскуларна пролиферација препокриена со конјунктивален епител.

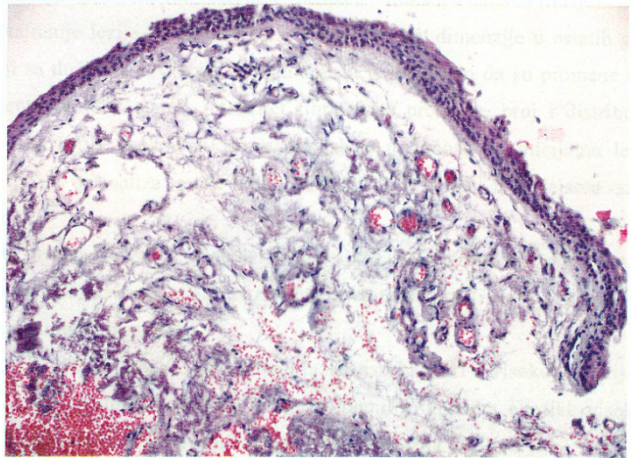
Анализирани се тангенционални пресеци на рецидивантни птеригиуми со аксијална должина поголема од 3 мм се до 6 мм.

Кај различни пресеци на иследуваните рецидивантни птеригиуми, бројот, големината и видот на крвните садови се разликува. Во близина на базалната мембрана на епителот се лоцирани бројни капилари со што се овозможува активно пренесување и доставување на потребните субстанции во епителните клетки со цел да се зголеми нивната митотска активност (сл.3, сл.4). Зголемениот број на крвни садови го зголемува крвниот доток и го активира процесот на мултиплицирање. Одредени крвни садови имаат тенденција за тромбозирање, или веќе се тромбозирани , или пак имаат тенок ѕид, а во одредени зони може да се забележи и крвна екстравазација. Освен карактеристичните капилари , се среќаваат и такви со поголем лумен и бројни анастомози со изглед на новоствoрени крвни садови.

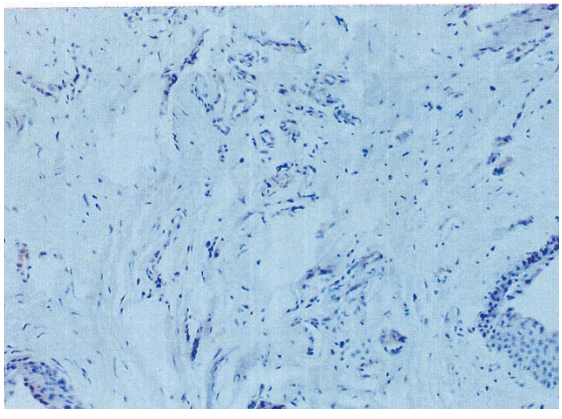
Бројот, луменот и видот на крвните садови се со изразена варијабилност кај рецидивантните птеригиумии, а и кај различни пресеци на еден ист птеригиум (сл.4) Кај сите иследувани птеригиуми бројот на крвни садови е поголем отколку кај контролната здрава конјунктива. Нежната капиларна мрежа на мултипни крвни садови со дискретно изразена фибриноидна промена во едематозната строма се забележува кај стационарните рецидивантни птеригиуми, додека комплексно богато разгранување на развиените капилари со поголем лумен е знак на прогресивните рецидивантни птеригуми (сл.3).



Слика 2. Богато разгранети пролиферирани крвни садови со широк лумен и активирани ендотелни клетки кај рекурентен птеригиум. (CD 34 x 20)



Слика 3.Богати разгранети капилари со широк лумен кај прогресивен рецидивантен птеригиум (HE, 20x).



Слика 4.Васкуларна петелка во пределот на вратот, која се разгранува кон напреднатиот дел на рецидивантен птеригиум (HE, 10x).

ДИСКУСИЈА

Најчеста постоперативна компликација по хируршкото отстранување на птеригиумот е постоперативното повторување или рецидивирање на птеригиумот (3,4,5). Ниската честота на рецидивирање ја потврдува и истакнува ефикасноста на една хируршка метода (3,4,6,7) Честотата на рецидивирање е значително поголема по одредени хируршки метод на екцизија на птеригиум, наспроти ретките рецидиви по трансплантационите техники на птеригиум. Хируршката екцизија на птеригиум со автотрансплантација на конјунктива на местото на оголената склера е ефикасна метода(14) со ретки рецидиви. Рецидивите се почести кај прогресивните птеригиуми и се директно поврзани не само со растот и развојот, туку и со морфолошката градба на птеригиумот и со методот на хируршкиот третман.

Во медицинската литература нема податоци за поврзаноста на рецидивите и возраста на пациентите. Во нашето иследување на рецидивантните птеригиуми, рецидивите повторно се јавија кај помладите пациенти, но без статистичка значајност поради малиот број на рецидиви. И во литературата е опишано дека рецидивите се јавуваат кај помладата популација т.е. возрасната група до 45 години (15).Поголемиот број на рецидиви кај помладата популација е во период кога кај истата има одредена доза на оштетување на лимбусот од надворешните фактори, но и присутна способност на делба на фибробластите, додека кај постарата популација присутен е дегенеративниот процес.

Рецидивите се забележани кај група на пациенти чија професионална работа се изведува на отворено (земјоделци и работници), поради директното или кумулативно дејство на УВ радијација која го оштетува лимбусот.

Рецидивите се јавија кај пациентите со помала временска еволуција на птеригиумот. Може да се заклучи дека птеригиумите со брз и агресивен раст се предодредени за рецидивирање , но за ова нема податоци во литературата. Најчесто рецидивите повторно се јавија кај средно големите рецидивантни птеригиуми (3,0мм-3,5мм), но и за оваа статистички значајно не може да се говори поради малиот број на повторувачки птеригиуми (10 %).

Fuchs-овите дамки се чест наод кај пациентите со рецидивантен и прогресивен птеригиум. Со ова се потврдува значењето на Fuchs-овите дамки на прогресија за прогнозата и начинот на лекување, за кое зборува и Busacca (16) во своето иследување. Во нашето иследување каде беа иследувани само рецидивантните птеригиуми можеше да се забележат Fuchs-овите дамки кај повеќето случаи и тоа кај повекегодишно перзистирачки рецидивантни прогредирачки птеригиуми кои зафаќаа повеќе од 3 мм од лимбусот на роговицата. Кај пациентите кои професионалната работа ја извршуваат на отворено и се подложени на надворешни влијанија, Fuchs-овите дамки на прогресија се почести. Од надворешните влијанија најголема улога има УВ зрачењето кое се поврзува со фокалната лимбална инсуфициенција (17). Во литературата, Fuks-овите дамки се поврзуваат со повозрасните пациенти заради што може да се поврзат со одредени сенилни дегенеративните заболувања на окото(Stoker-ova, Hadson-Stalisova линија)(18)

Штокеровата линија е вториот карактеристичен знак за прогресивноста на птеригиумот. Често се забележува жолтеникава пигментна линија , Stoker-ова линија, во меланодермот и истата настанува од пигментот хемосидерин кој се содржи во епителот на конјунктивата (19).Кај рецидивантните птеригиуми исто како и Fuks-овите дамки и Штокеровата линија е чест наод кај подолго перзистираните рецидивантни птеригиуми.

Хистоморфолошки, птеригиумот може да се дефинира како фиброваскуларна пролиферација покриена со конјунктивален епител.

Fuchs, е првиот автор кој ги опишал патохистолошките карактеристики на птеригиумот во литературата уште во 1982 година.Тој ги забележал густите задебелени еластични влакна, и промените во епителот на птеригиумот заедно со конкраментите но и хијалината дегенерација на субепителното сврзно ткиво (20).

Austin со соработниците (21), ја опишале најчестата карактеристична хистопатолошка слика на птеригиумот, и ја нагласиле еластодисплазијата и еластодистрофијата, која е резултат на УВ-радијациа која делува на активираните или оштетени фибробласти и ја зголемува нивната продукција и поделба.

Кај иследуваните птеригиуми во нашата студија, се покажа изразена варијација во бројот, волуменот и карактерот на крвните садови. Бројот на крвните садови е поголем кај иследуваните рецидивантни

птеригиуми отколку кај контролните примероци на булбарна конјунктива. Кај рецидивантните птеригиуми се забележани комплекси на крвни садови со богато разгранување и со поголем лумен што е карактеристична слика на временски подолга еволуција на птеригиуми со должина поголема од 3 мм. Поголемиот број на крвни садови и побогата крвна мрежа се забележаа кај хистопатолошките препарати кај пациенти кои се изложени на надворешни влијанија,кај земјоделци и работници.

Бројот на пресекот на крвните садови кај препаратите расте со возраста на испитаниците, иако таа корелација не е статистички значајна при нашето иследување. Присаството на крвните садови кај птеригиумот е поврзано со неговата активност (22), но поголемиот број на крвни садови на хистолошките препарати, може да е и поради стареење на конјунктивата која со годините стекнува се поголем број на неправилни и извијугани крвни садови(23).Меѓутоа, важно е да се истакне дека присаството на крвни садови е поврзано со непосредната активност на птеригиумот (пред или во тек на експанзивен развој(22). Оваа поврзаност е поочигледна при споредувањето на ангиогенезата на птеригиумот со други параметри на прогресивноста на птеригимот како што се зоните на прогресија или Штокеровата линија. Fuks-ови дамки се веродостоен показател на прогресивноста на птеригиумот и се во позитивна корелација со бројот на крвни садови. Сепак неможе да се повлече директна корелација помеѓу присаството на Fuks-ови дамки и процесот на васкулогенеза бидејќи истите се показатели на одреден период од растот на птеригиумот за чие напредување и формирање на ново сврзно ткиво неопходен е и поголем степен на васкуларизација или зголемување на бројот на новосоздадени крвни садови

Новостворените крвни садови беа подобро прикажани субепително, поради потребата за зголемување на епителната пролиферација која е овозможена со транспорт на неопходни материи преку циркулацијата односно преку новостворените крвни садови. Забележан е поголем број на крвни садови кај птеригиумите кај кои се јавил постоперативен рецидив на болеста но без статистичка сигнификантност, поради малиот број на рецидиви. Ова е очекувано бидејќи за создавање на ново сврзно ткиво на рецидивантниот постоперативен птеригиум потребен е и поголем број на крвни садови

ЗАКЛУЧОК

Рецидивантните птеригиуми се брзо растечки птеригиуми, со богато разгранета мрежа на крвни садови со голем лумен кои допринесуваат за брзо достигнување на големината на претходно ексцидираниот птеригиум кај помлади активни пациенти поради што повторно се нарушува видната острина и предизвикуваат естетски промени.

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Profesional paper

ПОВРЗАНОСТ НА ПОЛИМОРФИЗМОТ C677T ВО ГЕНОТ MTHFR СО БЕЛОДРОБНАТА ЕМБОЛИЈА

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АПСТРАКТ

Белодробната емболија е релативно чест клинички ентитет проследен е со висок морталитет, па претставува дијагностички и тераписки предизвик. Досегашните студии укажуваат на постоење на генетска поврзаност на определени тромбофилии со појавата на белодробна емболија ,вклучувајќи ги полиморфизмите во генот за метилен-тетрахидрофолатредуктазата (MTHFR).

Генетските анализи покажаа дека постои статистички сигнификантна поврзаност на хомозиготниот генотип TT, односно на алелот T, со белодробната емболија. Носителите на овој генотип, односно алел, имаат 4,4 пати, односно, приближно 2,5 пати, соодветно, повисока веројатност од белодробна емболија во однос на носителите на хомозиготниот генотип CC или хетерозиготниот CT, односно на алелот C.

Ваквите резултати се конкордантни со дел од објавените клиничко-генетски студии со сличен дизајн и укажуваат на потенцијалната употребливост на овој генски маркер во предикцијата на ризикот од белодробна емболија и текот на болеста.

Клучни зборови: белодробна емболија, тромбоемболизам, MTHFRC677T, генски полиморфизми

ВОВЕД

Белодробната емболија е релативно чест клинички ентитет проследен е со висок морталитет кој претставува дијагностички и тераписки предизвик. Преставува нарушување на белодробната циркулација поради присуство на тромби во артерија пулмоналис и нејзините гранки .Се смета дека има мултифакторијална и комплексна патогенеза, а во последниве дваесетина години екстензивно се проучуваат генетските фактори.

Кардиоваскуларните ризик-фактори (длабока венска тромбоза, историја на хипертензија и кардио- и цереброваскуларни инциденти) се значајно поврзани со појавата на белодробна емболија. Сепак, кај многу пациенти со сериозни ризик-фактори, какви што се масивните и долготрајни длабоки венски тромбози, не се јавува пулмонална емболија, додека кај некои пациенти истата настапува дури и при многу побанални

причини. Таквите дискрепанци силно суигерираат на влијанието на генетските фактори, особено што и ризикот од повторна белодробна емболија е повисок кај индивидуите со фамилијарна анамнеза за овој клинички ентитет.

Досега се вршени голем број на генетски истражувања на определени тромбофилии кои се почесто поврзани со белодробната емболија, вклучувајќи ги полиморфизмите во генот за метилентетрахид рофолатредуктазата (MTHFR) (1). Овој ензим врши фолат-зависна хомоцистеинска реметилација, која катализира редукција на 5,10-метилтетрахидрофолат во 5-метилтетрахидрофолат. Единечната супституција на базен пар на нуклеотидната позиција 677 (тимин наместо цитозин:677 C>T) во генот MTHFR резултира со супституција на аланин со валин на позиција 223 (A223V) во 5,10-метилтетрахидрофолатредук тазата со намалена активност што предизвикува хиперхомоцистинемија. Како резултат, овие лица се со повисок ризик од тромбоза. Околу 11% од белата популација е хомозигот за ова мутација, со тројно зголемен ризик од тромбоза. Иако ова е најчестата мутација, опишани се најмалку 40 различни мутации на генотMTHFR кај лица со хомоцистинурија. Стекнати причини за хиперхомоцистинемија вклучуваат недостаток на витамин B6, витамин B12,и недостаток на фолати, како и ренална инсуфициенција. Комбинирана фолна киселина – витамин B терапијата може да го намали нивото на хомоцистеин во крвта (2).

ЦЕЛИ

Основната цел на овој труд е да се испита поврзаноста меѓу фреквенциите на генотиповите и алелите на полиморфизмот rs1801133 (677 C>T) во генот MTHFR со белодробната емболија.

Целта на студијата вклучува и определување на веројатносната шанса за појава на белодробна емболија која може да укаже на потенцијалната употреба на превентивни и терапевтскки мерки за спречување или одложување на овој сериозен клинички ентитет.

МАТЕРИЈАЛ И МЕТОДИ

Во прелиминарната фаза од студијата, анализирани се 31 пациент со клинички докажана белодробна емболија, селектирани според критериуми за вклучување и за исклучување, какои 24 контролни испитаници кои немале анамнестички податоци за тромботични состојби. Кај сите вклучени пациенти КТ ангиографијата беше метод на избор за детекција на емболус во главните лобарни или сегментни пулмонални артерии .

Од секој пациент се колектирани селектирани демографски податоци (пол, возраст, образовно ниво, тип на професија, историја на пушење, консумација на алкохол, дислипидемии, хипертензија, фамилијарна историја за тромботични состојби, користење на орални контрацептивни средства и др.), лабораториски вредности (тромбоцити, коагулациски статус, D-димери, тропонин и др.), како и клинички податоци (коморбидитети и ризик-фактори, селектирани вредности од CT-ангиографија на белодробните артерии, ехокардиографија, Доплер-ултрасонографија на крвни садови, пресметани бодови според Wells-овата и/или ревидираната Женевска скала, податоци за лекувањето, терапискиот одговор и клиничкиот исход).

Податоците се земани само од пациенти на кои, по детално објаснување на постапката, целите, и нивните права, своерачно потпишале писмена согласност. Дозвола за користење на материјалите и податоците од пациентите во студијата е добиена од Етичката комисија за истражувања на луѓе при Медицинскиот факултет во Скопје.

Изолацијата на геномска DNA е вршена со методот на исолување со натриум хлорид, екстракција со хлороформ и последователна преципитација со етанол (3). Молекуларните анализи на определување на полиморфизмите во генот MTHFR се вршени со генотипизација користејќи TaqMan-флуоресцентни сонди со нуклеотидна секвенца специфична за амплифициран регион од соодветниот ген, обележани на 5›-крајот со флуоресцентниот обележувач FAM или VIC, додека на 3›-крајот со избледувачот NFQ. Нуклеотидните секвенци на прајмерите и на TaqMan сондите за генот MTHFR се според студијата на Yang со сор., 2013 (4). Отчитаните криви се анализирани со софтверот StepOne (Applied Biosistems) кој е интегрален дел од системот со методот на алелна дискриминација, со што е определен генотипот на испитуваниот полиморфизам.

Фреквенциите на генотиповите и на алелите од полиморфизмите во испитуваниот ген се анализирани со Fisher-овиот егзактен тест. Според овие податоци е

пресметан односот на шанси - oddsratio. Пресметките на интервалот на доверливост CI (confidence interval) се вршени при 95%, односно при p<0,05.

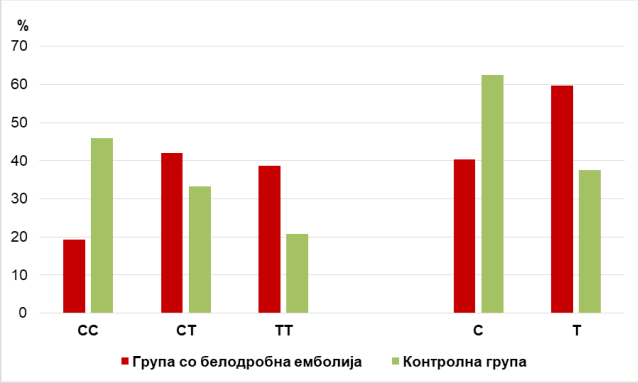
За статистички сигнификантни се сметаат вредностите на p<0,05, додека за високо сигнификантни тие p<0,01. Статистичките пресметки се вршени со користење на софтверските додатоци XLSTAT 2016, RealStatistics 2015 и GenAlEx 6.5 инсталирани на Microsoft Excel 2016.

За потребите на овој труд , прикажани се дел од добиените резултати.

РЕЗУЛТАТИ

Во текот на оваа фаза од изработката на студијата, досега се колектирани податоците и примероците од вкупно 31 пациент со белодробна емболија, од кои 13 (41,94%) се со машки, а 18 (58,06%) се со женски пол и имаат просечна возраст од 58,26 ± 13,15 години (опсег 31-78). Според обработените резултати, речиси половината од пациентите се изјасниле дека се непушачи, како и дека никој од нив не консумира алкохол. Повеќе од 80% од нив немале анамнестички податоци за претходна белодробна емболија, ниту еден немал тромбофлебитис, но речиси две третини од сите пациенти имале длабока венска тромбоза. Историја за акутен инфаркт на миокардот постои кај 6,5% од пациентите, исто колку и за исхемичен мозочен удар. Артериска хипертензија имале околу една третина од пациентите, дислипидемија 42% и дијабетес тип 2 13%. Анамнестички податок за хронично бубрежно заболување дал само еден пациент, додека ниту еден немал анамнеза за хепатални заболувања.

Застапеноста на генотиповите и на алелите на полиморфизмот rs1801133 (677 C>T) во генот MTHFR кај групата пациенти со белодробна емболија и кај контролната група е прикажана на графиконот 1.



Графикон 1. Дистрибуција на фреквенциите на генотиповите и алелите на полиморфизмот rs1801133MTHFR (677 C>T)

Резултатите од анализата на фреквенциите на генотиповите и на алелите на полиморфизмот rs1801133 (677 C>T) во генот MTHFR кај групата пациенти со белодробна емболија и кај контролната група се прикажани во табелата 1.

Табела 1. Анализа на разликите во фреквенциите на генотиповите и алелите на полиморфизмот rs1801133MTHFR (677 C>T) меѓу групата со белодробна емболија и контролната група

MTHFRrs1801133 (677 C>T)	Група со белодробна емболија		Контролна група		Chi-квадрат *	Однос на шанси
Генотипови	n	%	n	%	p	OR (95% CI)
CC	6	19,35	11	45,83	/	реф.
CT	13	41,94	8	33,33	0,103	2,979 (0,79 - 11,25)
TT	12	38,71	5	20,83	0,039	4,400 (1,04 - 18,60)
Вкупно	31	100,00	24	100,00		
Алели	n	%	n	%	p	OR (95% CI)
C	25	40,32	30	62,50	/	реф.
T	37	59,68	18	37,50	0,021	2,467 (1,14 - 5,35)
Вкупно	62	100,00	48	100,00		
* двонасочен						

Пресметките со генотипскиот и алелниот модел покажаа дека постои статистички сигнификантна поврзаност на хомозиготниот генотип ТТ, односно на алелот Т, со белодробната емболија. Носителите на овој генотип, односно алел, имаат 4,4 пати, односно, приближно 2,5 пати, соодветно, повисока веројатност од белодробна емболија во однос на носителите на хомозиготниот генотип СС или хетерозиготниотСТ, односно на алелотС. Разликите во однос на присуството на алелотТ меѓу групата пациенти со белодробна емболија и кај контролната група е анализирана и со адитивниот генетски модел, користејќи го двонасочниот Cochran-Armitage тест, а резултатите се прикажани во табелата 2.

Табела 2. Анализа на разликите во фреквенциите на алелите на полиморфизмот rs1801133MTHFR (677 C>T) меѓу групата со белодробна емболија и контролната група со адитивниот генетски модел

Број на алели MTHFRrs1801133 (677 C>T)	Група со белодробна емболија		Контролна група		Cochran-Armitage тест * p
0 T	6	19,35	11	45,83	0,038
1 T	13	41,94	8	33,33	
2 T	12	38,71	5	20,83	
Вкупно	31	100,00	24	100,00	

* двонасочен

Од табелата е видливо дека со оваа генетска анализа е најдена корелација меѓу бројот на алелиТ и појавата на белодробнаемболија. Статистичката веројатност за белодробна емболија повеќе од двојно се зголемува со присуството на алелот Т во генотиповите на пациентите со белодробна емболија (p=0,038).

ДИСКУСИЈА

Во овој труд е презентирана анализата на прелиминарните резултати од 31 пациент со белодробна емболија и од 24 контролни испитаници.

Анализите укажуваат на генетска поврзаност на полиморфизмот rs1801133 (677 C>T) во генот MTHFR со појавата на белодробна емболија. Таквиот наод е досега забележан и во голем број на слични клинички студии чии резултати се објавени во последниве десетина години. Така, во студијата на Hosseini со сор. (2015), била анализирана група на 182 пациенти со белодробната емболија како и контролна група од 250 испитаници во однос на присуството на неколку генски полиморфизми, вклучувајќи го и полиморфизмот кој е предмет на оваа семинарска работа (5).

Во однос на овој генетски маркер, авторите на трудот пресметале дека постои статистички високо сигнификантна поврзаност на присуството на варијантниот или хетерозиготниот генотип на овој полиморфизам со белодробната емболија. Попрецизно, присуството на овие поломорфнигенотипови е поврзано со околу 6 пати повисока веројатност од појава на белодробна емболија отколку присуството на дивиот генотип СС.

Поврзаноста на полиморфизмот С677Т во генот MTHFR со белодробната емболија е истражувана и во студијата на Basol со сор. (6). Анализата на 118 пациенти со белодробна емболија и 126 контролни испитаници покажала дека не постои поврзаност на генотиповите, туку со алелната фреквенција на овој полиморфизам со веројатноста од појава на белодробна емболија. Имено, носителите на варијантниот алел Т имале 57% повисока шанса за белодробна емболија отколку кај носителите на алелот С и оваа разлика била статистички сигнификантна.

Од друга страна, постојат и спротивни наоди во голем број објавени клинички истражувања. На пример, во метастудијата спроведена од Simone со сор. во 2013 година, анализата на претходно објавени податоци од 31 студија покажале дека нема сигнификантна поврзаност на полиморфизмот MTHFR 677 C>T со белодробната емболија (7). Ваквата дискордантност може да се должи на голем број интринсични и надворешни фактори, вклучувајќи ги епистатските ефекти на полиморфизмите и мутациите во други гени кои се почесто застапени во определени етнички групи, разликите во критериумите за вклучување и исклучување меѓу разните студии, енвиронменталните, нутритивните и други фактори.

Се претпоставува дека термолабилната форма на ензимот MTHFR предизвикува хиперхомоцистеинемија и други тромбофилични промени кои ја зголемуваат шансата за тромботични состојби и до емболуси во пулмоналната циркулација (8). Кај индивидуите кои се хомозиготни за варијантниот, мутиран тип на овој полиморфизам, односно содржат две алели со нуклеотидот Т на позицијата 677: ТТ, кодираниот варијантен протеин има само околу 30% од ензимската активност, а хетерозиготните индивидуи со генотип СТ имаат приближно 65%, во однос на индивидуите

кои се хомозиготни за дивиот генотип: CC.

Важноста од потенцијалната клиничка употребливост на овој генетски маркер не е само во однос на проценката на ризикот од појава на белодробна емболија, туку и во однос на терапискиот одговор. Постојат податоци дека пациентите со белодробна емболија кои се носители на полиморфниот генотип TT се екстремно резистентни кон антикоагулантната терапија (9).

Сите овие податоци укажуваат на можната апликабилност на користењето на полиморфизмот C677T во генот MTHFR како генетски маркер за белодробната емболија.

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Profesional paper

ANXIETY IN ACUTE MYOCARDIAL INFARCTION SURVIVORS

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ABSTRACT

Introduction :Data obtained in some studies indicate that somatic disorders, in a certain percentage, are associated with a mental health problems, whether in a form of two co-existent diseases, whether psychological problems are only associated symptoms and/or response to somatic disease. Anxiety is psychological symptoms frequently encountered in patients suffering from acute myocardial infarct (AMI). The AIM of our study was to determine the percentage of anxiety in two investigated groups of patients with myocardial infarction and to determinate the correlation between socio-demographic characteristic and level of anxiety in survivors of AMI. Material and methods: The study was designed as observation cross-section including 80 patients treated at the university Clinic of Cardiology Skopje , observed as 2 groups : group 1 was presented with patients during hospitalization for AMI, and 2 group were patients survivors after 6 months of the acute coronary event. Anxiety status was assessed using HAMA scale. Results : The two groups of patients did not show significant difference according distribution of gender , smoking , physical activity, stress , age, mean HAMA , BMI , age of education and marital status . In the first group 21 (51,2%) of patients have anxiety symptoms while in second group 25 (64,1%). In our study acute MI was more prevalent in a men but women had a higher risk of anxiety disorders 27,3% v.s (22,7%). In examination groups the anxiety (HAMA score) was positive correlate with socio-demographic and clinical parameters where only we got negative correlate between anxiety with marital status and BMI in the first group and negative correlation with married status, smoking status, physical activity, stress and BMI in the second group . .Conclusion: The results in our study showed indicative representation of anxiety in patients survivors of AMI. So screening for anxiety in all AMI patients is also important because this patients should be treated differently than those who are not anxiety.

Kay words: patients, myocardial infarction, anxiety, therapy

INTRODUCTION

Data obtained in some studies indicate that somatic disorders, in a certain percentage, are associated with a mental health problems, whether in a form of two co-existent diseases, whether psychological problems are only associated symptoms and/or response to somatic disease. Anxiety is psychological symptoms frequently encountered in patients suffering from acute coronary syndrome. It is believed that the prevalence of anxiety among cardiac patients is between 15 and 50% (1,2). Several studies have demonstrated increased risk of sudden cardiac death in patients with phobic, generalized anxiety and panic disorders (3,4). Anxiety increases the mortality rate in patients with heart diseases, by increased the risk from ventricular arrhythmias and sudden cardiac death, consequently (5). Continuation of exhibiting a high level of anxiety after the diagnosis of coronary artery disease is a significant risk factor for the development of myocardial infarction or death in these individuals (6). Several mechanisms explain this finding including links between negative emotions with bad habits such as smoking, nutritional habits, reduction of physical activity. Moreover post MI depression or anxiety predicts poor quality of life (7). Also emotional stress has the direct

negative effect on the progression of atherosclerosis and it reduces threshold for ventricular arrhythmias and possibly sudden cardiac death (8). Anxiety increases blood coagulability during and after emotional stress which is one of the mechanisms and may link this emotion and cardiac disease (9). Cerebral atherosclerosis may facilitate anxiety and depressive symptoms even before generating cardiac ischemia creating a spurious circulars virtuous (10). However , hypothalamic-pituitary-adrenal (HPA) axis deregulation may trigger the onset of depression or anxiety (11,12). Moreover, both anxiety and depression can affect cardiac prognosis by activating the HPA axis and rennin-angiotensin-aldosterone system, increasing the risk of reduce heart rate variability and baroreflex cardiac control and increasing the inflammatory response platelet reactivity (13,14,15). Because anxiety share pathophysiological mechanisms with cardiac events, the possible relationship among anxiety and post MI should be investigated. Myocardial infarction is associated with an increased risk of anxiety and depressive disorders during the first 2 years of follow-up so, post-MI anxiety and depressive disorders increase the risk of subsequent cardiac events (16,17). Anxiety is one of the established risk factors for sudden cardiac death so differentiated approach to diagnosing and treating anxiety in post AMI patients is warranted (4,5).

AIM

The AIM of our study was to determine the percentage of anxiety in two investigated groups of patients with myocardial infarction and to determinate the correlation between socio-demographic characteristic and level of anxiety in survivors of AMI.

MATERIALS AND METHODS

The patients of this cross section study were examination in the University Clinic of Cardiology Skopje. The study was approved by the regional ethics committee for research. All participants gave written consent. We evaluated prevalence of anxiety in 80 patients survivors of AMI aged 45-64 years.. The patients were observed in two examination groups: the first group (N=41) was presented with patients during hospitalization for AMI, the second group (N=39) were patients after 6 months of the acute coronary event. For the collection of data we used medical documentation (history of illness and an outpatient diary). The socio-demographic data included this analysis : age, gender, marital status , education (years of schooling) The life-style characteristics were analyzed evaluating tobacco smoking status (smoker, non-smoker), psychical activity, stress. In our study we also evaluated body mass index (BMI). Anxiety symptoms was measured using the Hamilton Anxiety Rating Scale (HAMA). The HAMA is self –report 14-items screening instruments used to screen for assess the severity of anxiety symptoms The total HAMA scores was ranges from 0-30 (<17 –mild severity; 18-24 mild to moderate severity; 25-30 moderate to severe severity anxiety symptoms). , Acute myocardial infarction was diagnosed according to the European society of cardiology consensus guidelines. Criteria for AMI included specific clinical symptoms according to case history information (typical chest pain , changes in blood levels of cardiac enzymes and specified ECG changes). We excluded participants with cancer, asthma, diabetes mellitus, other endocrine disorders and autoimmune diseases, also and participants who use anti anxiety or antidepressant agents The differences between observed groups were tested with Chi-square (categorical data) and analysis of variance (ANOVA) for continuous variables and using T student test to define the significant inter groups difference. The correlation between HAMA score and the socio-demographic and clinical parameters was tested with p- Spearmen coefficient. The data analysis were performed using SPSS for Windows (ver25)

RESULTS

The two groups of patients did not show significant difference according distribution of gender (X^2=2,360, df=2, P>0,05) smoking (X^2=1,735, df=2, P>0,05) physical activity(X^2=5,920 df=2, P>0,05), stress (X^2=4,369, df=2, P>0,05), age(F=1,359 df=2, P>0,05), mean HAMA (F=0,150 df=2, P>0,05), BMI (F=0,012 df=2, P>0,05), age of education(F=0,994 df=2, P>0,05)and marital status (X^2=5,315 df=2, P>0,05). (Table 1)

Table 1. Socio-demographic and clinical characteristics of patients who survived acute myocardial infarction

Parameter	Group 1 (N=41)	Group 2 (N=39)	p
Gender (m/f)	70,7/29,3	84,6/15,4	ns
Age (years)	63,5±6,2	61,4±9,2	ns
HAMA(score)	15,6 ±3,9	16,3±4,4	ns
Smoking (Y/N)%	66,7/33,3	62,2/37,8	ns
Physical activity (Y/N)%	36,6/63,4	53,8/46,2	ns
Stress (Y/N) %	78,0/22,0	74,4/25,6	ns
BMI (kg/m2)	26,2±4,1	26,30±4,3	ns
Marital status M/S(%)	82,9%17,1%	92,3%/7,7%	ns
Education (years)	11,1±2,82	10,26±2,009	ns

There was no significant difference in distribution according HAMA score in patient survivors of AMI between obserevd groups (Table 2). In both groups there were no patients with .intensive anxiety. In the first group 21 (51,2%) of patients have anxiety symptoms while in second group 25 (64,1%)..

Table 2. The distribution of survivors of AMI according their HAMA score in the observed group

HAMA score	Group 1 (N=41)		Group 2 (N=39)		P level
	N	%	N	%	
No anxiety	20	48,7	14	35,9	ns.
Mild	18	43,9	20	51,2	
Mild to moderate	3	7,3	5	12,8	
Moderate to severe	0	0	0	0	

Data obtained from all groups show significant positive correlation with anxiety in female patients. Moreover, there was positive but insignificant correlation of the patients' age with anxiety in the observed groups. Smoking was positive insignificant correlation with anxiety in the first group but in second group was significantly negatively correlation with anxiety. Physical activity was significantly positive correlation with anxiety in patients during acute coronary event but negative insignificant correlate in survivors after 6 month of AMI (Table3,4). The group 1 showed insignificantly positive correlation of education and stress with anxiety and insignificantly negative correlation of marital status with anxiety. (Table 3). The group 2 presented negative insignificant correlation with anxiety according stress and marital status but significant correlation with anxiety in this group presented only BMI (negative) and education (positive) (table 4).

Table 3. Correlation of the socio-demographic and clinical parameters with anxiety observed in patients during acute coronary event. .

Parameters	p-Spearmen coefficient	p valvule
Gender (female)	0,360	0,003
Age	0,079	0,084
Smoking	0,270	0,064
Physical activity	0,311	0,002
Stress	0,070	0,082
BMI	-0,320	0,007
Marital status	-0,072	0,092
Education	0,280	0,091

Table 4. Correlation of the socio-demographic and clinical parameters with anxiety observed in patients after six months after acute coronary event. .

Parameters	p-Spearmen coefficient	p valvule
Gender(female)	0,366	0,002
Age	0,290	0,098
Smoking	-0,550	0,003
Physical activity	-0,302	0,063
Stress	-0,210	0,092
BMI	-0,605	0,003
Marital status	-0,062	0,072
Education	0,365	0,001

DISCUSSION

The results in our study between examination groups of patients did not show significant differences according socio-demographic and clinical characteristic. Distribution of gender (X^2=2,360, df=2, P>0,05) smoking (X^2=1,735, df=2, P>0,05) physical activity(X^2=5,920 df=2, P>0,05), stress (X^2=4,369, df=2, P>0,05), age(F=1,359 df=2, P>0,05), mean HAMA (F=0,150 df=2, P>0,05), BMI (F=0,012 df=2, P>0,05), age of education(F=0,994 df=2, P>0,05)and marital status (X^2=5,315 df=2, P>0,05).

The present study revealed that 51,2% of patient in the first group have mild and mild to moderate score of anxiety . This results correlate with some study who reported that division according to the levels of anxiety ,in a groups without the anxiety and intensive anxiety there were no patients, while in the group with mild anxiety there were 70% of patients and 30% had moderate anxiety (17). But this results not correlate with some research who reported anxiety disorders in 17,26% of post MI patients (18) , and 18,5 % in Netherland study (19). The results in second group reported that that 64,1% of patients have anxiety symptom this results not correlate with another study who reported that 11,9% of patients have anxiety after 6 month of AMI (2),and 18,7% after 3 month of AMI (20). The results obtained in our study are still indicative for the relationship between anxiety and coronary heart disease (AMI), so they report that anxiety symptoms associated with risks for AMI. This results correlate with another research who reported that maybe anxiety influence for the development of coronary artery disease. A meta-analysis of 5750 patients with MI also demonstrated that patients with anxiety are at risk of adverse cardiac events and all cause mortality (21). Several studies have demonstrated that the anxiety is the

most common psychological symptoms in patients with AMI (22,23). Some findings reveal that MI is risk factor for clinical anxiety during the first 2 years and also post MI anxiety increases the risk of recurrent MI (24) and anxiety disorders are associate with a higher mortality rate (25,26). So because patients with MI is associated with an increased risk of anxiety so this patients mast requiring psychiatric treatment.(2)In our study acute MI was more prevalent in a men but women had a higher risk of anxiety disorders 27,3% v.s (22,7%). Similar results have been reported in several studies (26,27,28). A cross –section study in Norway indicated that more women reported anxiety , sleep disturbances and high family stress than men in the year prior to first time (29). A meta analysis also revealed that biological factors (hormones) and psychological factors (role overload) possibly explain the significantly higher burden of emotional distress in women with coronary artery diseases then men (26). Therefore gender roles may majorly influence post-MI recovery .Statistically significant positive correlation was found in our study between anxiety and age, this results correlate with another study (1,2,3). This means that we can expect that elderly have a higher intensity of anxiety and consequently a higher risk for adverse outcome. Sex and age- stratified analyses show that women and patients aged 45 to 64 years had a higher risk of anxiety and depression (2). Another finding in our study is that middle-aged patients(45-64) years with stress work had a higher risk of anxiety disorders . Previous studies demonstrated that young and middle aged patients experienced higher stress after acute MI (24,25). Age may be a crucial factor influencing the relationship between post- MI survivors were the main income earners in their families, they also must cope with demands associated with physical changes , which may affect personal and social life, leading to a decline in work performance (27). Some authors examined the risk factor for the psychological distress and the behavior factors to heart disease separately for different groups and found that unemployment and serious psychological distress were associated with heart disease patients <65 years. (29). The illness perceptions of post-MI patients are associated with lower mental and physical health-related quality of life (2).Therefore supporting post MI patients in improving their perception of personal control may affect their personal and social lives, particularly in middle age. Furthermore patients with post-MI anxiety disorders, have a higher risk of recurrent MI. The prevent adverse cardiac events, patients with acute MI should be earlier assessed to identify post-MI psychological distress and provide age and sex-specific care (26). Many prospective studies of anxiety and AMI risk failed to adjust even for well-know cardiovascular risk factors such as smoking and physical activity (3,4) Smoking was positively correlated with anxiety affect among patients in our study. This is undoubtedly related to the fact that patients with anxiety are three times more likely to be cigarette smokers (12). So in our study smoking was positive and insignificantly associated with anxiety in patients during acute coronary event, but in survivors of AMI after 6 month of AMI smoking was significantly negatively associated with anxiety. This result is most likely due to the internist's recommendations that it should be stopped by smoking cigars after AMI. However, the higher prevalence of anxiety in women and smoking positively correlation with anxiety and it is important because anxiety affect might act to foster coronary disease and early mortality (20,26)..In our study we got negatively association between anxiety and BMI in both examination groups. The results obtained are most likely due to the regular treatment of the prescribed therapy as well as the medical recommendations surrounding the correct diet. Physical activity was significantly positive associated with anxiety in the first group of our study while in second group it was insignificantly negative associated with anxiety. These obtained results are most likely due to the inclusion of internists for reducing the physical activity after AMI. Some researches reported that between anxiety and marital status exit correlation (12), in our study we got negative correlation between marital status and anxiety also the large number of the patients with anxiety were with poor social support. An increasing number of data from prospective studies show that negative emotions such an anxiety are risk factor for coronary artery disease. Several mechanisms explain this finding including links between negative emotions with bed habits such as smoking, nutritional habits, reduction of physical activity (7,8). Statistically significant positive correlation was found between anxiety and age; bad habits (smoking, nutritional habits -BMI, reduction of physical activity . Also anxiety positively correlated with the number of hospitalizations due to CHD (r=0,432 p=0,019) (10,11). Based of these data we can say that the patients with higher number of hospitalizations due to higher intensity of current anxiety are at a higher risk of re-infarction and lethal outcome. Interestingly, patients who were extremely anxious basically have the lowest level of internal locus of control This fact can de-motivate

the patient to change behavior to that which will help to reduce the number of risk factors and reduce the likelihood of new coronary events. Further research is recommended in particular with older, female and lower socioeconomic status (10,11). Moreover post MI anxiety predict poor quality of live. (20). The results in some studies indicated that post MI patients have a high risk of receiving a new diagnosis of anxiety and depressive disorders during the first year of follow-up (2). However in our study we got a 51vs 61 percentage of anxiety conduction and this result is very important because anxiety symptomatology are associated with increase risk of MI and mortality in the patients with AMI . Some have argued that anxiety should be identified during the AMI hospitalization because anxiety patients have a higher risk of morbidity and mortality after AMI (3,4). Some researchers have shown that anxiety predict total mortality and the prognosis of patients after MI (1,2), but evidence concerning the role of anxiety in the pathogenesis of coronary disease has been less clear. Because the factor that has complicated research in this area is the similarly between the symptoms of anxiety and the symptoms of coronary disease. Therefore, it is important for studies to rely on hard outcomes such as documented AMI (4). A second solution is to eliminate somatic symptoms from consideration when anxiety is assessed (6). Cardiologists may be unable differentiate between somatic and psychological complaints when patients describe their illness experiences limiting referrals for psychiatrics. (28).Also those people who basically were very anxious, have the lowest level of internal locus of control which means that they think they have very low influence on the course and outcome of disease. This fact can de-motivate patient to change behavior that which will help to reduce the number of risk factors and reduce the likelihood of new coronary events (27,29).

CONCLUSION

In our study we got anxiety condition among post MI patients and these results are very important because anxiety symptomatology is associated with increased risk of MI and mortality in the patients with AMI. The beneficial effects of anxiety on cardiovascular mortality and morbidity suggest that a differentiated approach to diagnosing and treating anxiety in post AMI patients is warranted So screening for anxiety in all AMI patients is also important because that patients should be treated differently than those who are not anxiety. So the treatment anxiety with pharmacotherapy, psychotherapy and social support, lowering the risk of reinfaction or mortality and reduce the cost of medical care,

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Profesional paper

DYSMENORRHEA SYMPTOMS, INTENSITY OF PAIN AND COPING STRATEGIES AMONG STUDENT POPULATION IN REPUBLIC NORTH MACEDONIA

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ABSTRACT

Aim of this study is to present the symptomatology, intensity of pain as well as the coping practices among population of young university students in Republic of North Macedonia

A cross sectional study was conducted among 847 university students aged 19-23 years old. An instrument of the study was a specially designed Questionnaire which included the questions about the intensity of the pain measured by Visual Analogue Scale as well as the presence of specific symptoms marked on separately in a table.

Prevalence of dysmenorrhea is 72%. Our study showed that 52.5% of participants with dysmenorrhea had moderate pain with average pain score of 6.35 ±2.2 according the Visual Analogue Scale (VAS). 33% had severe pain with scores ≥ 8 on the VAS.

Most prevalent symptoms were: pain in lower abdomen (98%), lower back pain and malaise (76%), irritability 63%, headache 58%, myalgia 56%, vertigo 42%, nausea and vomiting 41%, diarrhea 32%, faintness 16%.

The VAS score severity of symptoms correlated significantly with the intensity of the each of the symptoms.

Most of the dysmenorrhea participants consulted a family member or a friend about the condition and only 14% of them visited a doctor.

Half of them took over-the –counter medications on their own opinion and bed-resting with warm compressions on lower abdomen were their choice for self-care management.

Dysmenorrhea is a frequent condition but seldom addressed adequately both by the patients and the professionals.

Keywords: primary dysmenorrhea; pain intensity; Visual Analogue Scale; self-care strategies

INTRODUCTION

The normal menstrual cycle starts and ends with the menses in absence of pregnancy. The decay of the endometrium triggers a chain of processes where prostaglandins play key role in the shedding of the endometrium and control the amount of flow during the menstruation. This is physiological process. Nevertheless, very often the balance is turned towards higher basal uterine tone, the contractions are more frequent and last longer, which results in ischemia and pain i.e. dysmenorrhea. Moreover the excess of prostaglandins synthetized could stimulate bronchioles, intestines and could cause contraction of smooth muscles of vessels and provoke bronchoconstriction, nausea, vomiting, diarrhea and hypertension (1). The symptomatology

can be of different extent and sometimes of debilitating nature and pose a need for medication, and can restrict the girls from everyday activities and school (2). The prevalence varies between 28% and 89.5%, depending on the author and the population studied (3). The perception of pain is individual and there are many ways to quantify the intensity of the symptoms. In the literature.there are self-reported pain perception scales such as the Visual Analogue Scale, Numeric Rating scale, Verbal descriptor Scale and others and algometry to measure the intensity of induced pain. (4) (5) (6) (7) (8) There are some researchers that even made a scoring system by scoring the intensity of each of the symptoms other than pain alone(7). On the other side the impact of the condition on everyday life is very strong (9) (10). The aim of our study was to investigate the implications of this condition in our population.

MATERIAL AND METHODOLOGY

This study was designed as a cross sectional observational study. An instrument was a specially designed Questionnaire which after the approval by the Ethics Committee of the Medical Faculty in Skopje, was disseminated among the female students in their first and second year of study. The students of medicine, informatics and security were addressed. The fulfillment of the questionnaire was during brakes between classes and the main investigator was on spot and available for clarifying. The participation was on a voluntary basis and no reward was offered.

The Questionnaire had several blocks of questions: beside demographic and epidemiological questions suggesting presence of risk factors for dysmenorrhea there were questions about personal and gynecologic history as well menstrual symptomatology. Those who answered positively for presence of dysmenorrhea, continued with the questions about the degree of pain, time of occurrence and duration, presence of other symptoms, the degree of impact on their everyday life and the coping strategies.

The pain was quantified with Visual Analogue Scale (VAS), a 10-centimeter long scale divided into 10 sections-1cm each, with mark 0 meant “NO PAIN” and 10 meant “STRONGEST, UNBERABLE PAIN”.

Second tool for quantification of the dysmenorrhea was a table in which the participants could express the presence of 10 other parameters except for the lower abdomen pain. At the same time, they could grade each of the symptoms as moderate, severe and very severe. These parameters were: lower abdominal pain, lower back pain, headache, nausea/vomiting, diarrhea, asthenia, irritability, vertigo, myalgia, collapse. Special attention was put on the influence of the symptoms on everyday activities. For the purpose of this survey we analyzed the correlation of the VAS score with the intensity of each of the symptoms.

At the end, a voluntary-basis consultation with a gynecologist was offered to each participant.

RESULTS

The results of the study of a cohort of 847 students, studying on 3 State universities in our country (medicine, security and informatics sciences) are presented below. The participants were aged 18-23 years. Dysmenorrhea is a common problem in our population with prevalence of 72,4%, meaning 613 out of 874 answered positively on the question about dysmenorrhea.

Nearly half of the students with dysmenorrhea (47 %), had pain during the first or the first and the second day of menses. Dysmenorrhea is more frequent between the students who answered that they have a member in the family with dysmenorrhea, meaning almost 84.5% had positive family history for dysmenorrhea ($p<0.001$).

The participants were offered a VAS, 0 to 10 scale on which they could quantify the severity of the pain during last 6 months. The zero mark meant no dysmenorrhea and 10 meant unbearable severe pain. The mean score of pain was 6.35 ± 2.2. Results from the Visual Analogue Scale for all participants in this study are presented in Table 1.

Table 1: severity of pain according Visual Analogue Scale

Severity of pain	Dysmenorrhea (%)
Mild (0-3)	63 (10.28%)
Moderate (4-7)	322 (52.53%)
Severe (8-10)	202 (32.95)
No data	26 (4.24%)

Beside VAS, a table of symptoms was offered to the participants. Pain in lower abdomen was dominant in 98.6% (579) cases and out them 29% (170) declared the pain as severe. The lower back pain was present in 76.2% (438) with mostly moderate intensity- 33.7% (194) of them.

General malaise was present in 76.2% (435) of dysmenorrhea participants and it was of moderate intensity in 39.9% (228).

Irritability was noted by 63% (354) participants and it was moderate in 28.5% (160).

During the menses 57.9% (338) participants had headache and 31.7% (185) described it as moderate

More than half, 56.5% (327) of the dysmenorrhea participants had myalgia declaring it as moderate in 32.3% (187).

Gastrointestinal symptomatology in the name of nausea, vomiting was reported by 40.9% (234), while fewer had diarrhea -32.6% (185). These symptoms were mostly with moderate intensity– 29.1% (166), 22.9% (130), accordingly.

Eighteen percent 18% (101) had faintness, while 41.6% (236) had vertigo.

The intensity of the symptomatology had been obstacle for normal everyday functioning in– 47.4% (213).

Table 2: Correlation between VAS score and separate symptoms

	Dysmenorrhea			p-level
	mild n (%)	moderate n (%)	severe n (%)	
Pain in lower abdomen				
yes	5 (93.22)	313 (99.37)	190 (98.96)	1vs2 p=0.0000 1vs3 p=0.0000 2vs3 p=0.62
no	4 (6.78)	2 (0.63)	2 (1.04)	
Lower back pain				
Yes	32 (57.14)	220 (71.66)	167 (87.89)	1vs2 p=0.03 1vs3 p=0.0000 2vs3 p=0.0000
No	24 (42.86)	87 (28.34)	23 (12.11)	
Headache				
Yes	20 (36.36)	177 (56.55)	124 (63.92)	1vs2 p=0.0056 1vs3 p=0.0003 2vs3 p=0.1006
No	35 (63.64)	136 (43.45)	70 (36.08)	
Nausea; vomiting				
Yes	7 (13.21)	97 (31.7)	121 (63.35)	1vs2 p=0.0061 1vs3 p=0.0000 2vs3 p=0.0000
No	46 (86.79)	209 (68.3)	70 (36.65)	
Diarrhea				
Yes	11 (21.15)	90 (29.22)	81 (42.63)	1vs2 p=0.23 1vs3 p=0.0047 2vs3 p=0.0022
No	41 (78.85)	218 (70.78)	109 (57.37)	
Malaise				
Yes	25 (46.3)	228 (74.27)	165 (86.84)	1vs2 p=0.0000 1vs3 p=0.0000 2vs3 p=0.0008
No	29 (53.7)	79 (25.73)	25 (13.16)	
Irritability				
Yes	18 (33.96)	189 (62.17)	136 (73.51)	1vs2 p=0.0001 1vs3 p=0.0000 2vs3 p=0.01
No	35 (66.04)	115 (37.83)	49 (26.49)	
Vertigo				
Yes	6 (11.11)	120 (39.09)	107 (56.61)	1vs2 p=0.0001 1vs3 p=0.0000 2vs3 p=0.0001
No	48 (88.89)	187 (60.91)	82 (43.39)	
Myalgia				
yes	15 (27.27)	165 (53.57)	133 (68.91)	1vs2 p=0.0003 1vs3 p=0.0000 2vs3 p=0.0007
No	40 (72.73)	143 (46.43)	60 (31.09)	
Faintness				
Yes	2 (3.7)	36 (11.88)	53 (28.8)	1vs2 p=0.073 1vs3 p=0.0001 2vs3 p=0.0000
No	52 (96.3)	267 (88.12)	131 (71.2)	

The table 2 shows the frequency and intensity of the symptoms accompanying menses, among different degrees of severity of dysmenorrhea.

The table shows the positive correlation of the VAS pain score with the severity of separate symptoms between mild, moderate and severe dysmenorrhea.

There was a separate question about the debilitating nature of the condition and we received answers that 18.4% (156) of them stay at home during the condition, 11.22% miss school, 13.11% sleep all the time, which all together gives us a score of 42.75% of the participants which are disabled for everyday activities. A small part of the participants -17.8% still go to school but with limited activities.

About the problem of dysmenorrhea 49.6% (420) of our participants have discussed with a family member (mother or sister), 24.2% (205) with a friend and the least of them, only 14.8% (125) consulted a professional.

Almost the half of the participants 49% (415) take an OTC medication mostly from NSAID group.,

Self-care strategies are employed by 63.2% (535) of the participants.

The tables that follow show the medication list and the self-care strategies employed.

Table 3: Medications

Do you use pain killers?	n (%)
yes	415 (48.99)
No	158 (18.65)
Missing	274 (32.35)
most used medications:	
ibuprofen lizinat	297
ketoprofen	89
nimesulide	41)
acetaminophen	23
metamizol	76
trospii chloridum	45
naproxen natrium	22
metamizol natrium+kofein+B1	10
ibuprofen + paracetamol	9
other	33

Table 4: Self-care strategies

Do you practice self-care?	n (%)
Yes	535 (63.16)
No	54 (6.37)
missing	258 (30.46)
Antalgic position and bed rest	346 (40.85)
Warm compressions on the abdomen	242 (28.57)
Cold compressions on the abdomen	14 (1.65)
Hot beverages tee	207 (24.44)
Cold beverages	6 (0.71)
Folk medicine	12 (1.42)
Homeopathy	3 (0.35)
Acupuncture	4 (0.47)
Massage	108 (12.75)
Hypnosis	1 (0.12)

DISCUSSION

Dysmenorrhea is a frequent condition in adolescent and young adult population. The prevalence in our study is 72.4% which is in harmony with the most of the literature(11) (12) (13) (14)1.05-2.13 (15)

According the pathophysiology the excessive prostaglandin synthesis is culprit of the intensity and accompanying symptoms(1)

According the Visual Analogue Scale, more than half of our participants (52.5%) gave mean pain score of 6.35±2.2, which means moderate pain, while 32.95% of our participants with dysmenorrhea had severe pain mean VAS score =8.3.

The table 2 shows high association of the intensity of each of the symptoms with the severity of pain scored on VAS. This can be a proof that VAS score of pain is an excellent tool to describe the intensity of the condition and should be routinely used, while the description of each of the symptoms should be used in further evaluation and addressing each one of them.

In the literature there is evidence of difference in uterine blood flow indices in the group of patients with primary dysmenorrhea compared to healthy controls. Further there were differences not only on the first day of cycle but throughout whole cycle. Therefore the conclusion that primary dysmenorrhea is a disease of the whole cycle. (16) (17) The evident vasoconstriction was a promotor of excess prostaglandin synthesis in circulation which lead to the extra genital symptoms like nausea, vomiting,

diarrhea, faintness.

The timeframe of the symptom occurrence is set at the onset of the menstrual bleeding and last mostly the first and the second day which corresponds to the data in the published literature(18)

The extent of restriction in the everyday activities as a result to dysmenorrhea gives us the impact of this condition- Almost half of the participants have restriction in their activities and miss school/classes, a small number still attend school but with limited activities(19) . This fact alone as well as the repetitive nature of the condition brings the young person in emotional distress and lower the quality of life.

The positive familial history of dysmenorrhea showed to be very significant. There can be a pattern of learned and empirical behavior in the management of pain. It is the root cause of the "minimizing" the severity of the condition by the patients and thus it's underreporting.

About the problem of dysmenorrhea half of our participants talked to a family member and 24.2% to a friend. Only 14.7% consulted a professional!! This is a proof of the low level of gynecology visits by this age group which may be due to stigma, shame and low level of trust. Similar results have been published by several international studies (20) (21) (19)

Half of our participants consume medication, on their own and mostly OTC medications of the NSAID group. This is at least incorrect use and leads to inadequate therapeutic effect, but sometimes may lead to side effects.

However, 42.17% of our participants consider that they either don't or at least partially address the problem with success.

The self-care strategies depend on the cultural and sometimes social background (22) (23) (24). Among our students the most used self-care methods were antalgic position, bed rest and warm compressions on lower abdomen, as well as hot beverages- tee and more seldom massage. There were only 3 using homeopathy and 4 students using acupuncture to alleviate symptoms which means allopathic medicine is strongly established or there is no information about other kinds of treatments provided to our population.

The importance of addressing the issue of primary dysmenorrhea is forthcoming according latest research (25) They researched a large number of pregnancies and the newborns with a long term follow up till age of 12 and concluded that the women with primary dysmenorrhea pre-conception had higher risk of developing psychological distress during third trimester and puerperium. The severity of the dysmenorrhea correlated to the severity of the distress.

CONCLUSIONS

Dysmenorrhea is very common problem of the young adult and adolescent population, still insufficiently addressed by the patients and the professionals.

Visual Analogue Scale is an excellent tool to measure the intensity and severity of the symptoms.

Part of the patients follow the pattern of the female members of the family and consider that they should deal with stoicism beside the distress they suffer. The other part takes advices from unfit counselor and considers taking pain medication is appropriate. This may have consequence inadequate medication, un proper dosage and unwanted treatment effects.

On the other hand the professionals should pay more attention to this otherwise healthy population, to meet their needs and to disseminate health knowledge to prevent further implications to their future reproductive life.

From public health point of view it is necessary to employ the policies for promotion of healthy life-styles and health information for this population.

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Profesional paper

ANTHROPOMETRIC CHARACTERISTICS OF SCHOOLCHILDREN AND ADOLESCENTS IN THE TETOVO REGION

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ABSTRACT

Objectives: Measuring the anthropometric characteristics in childhood and in adolescence are the most common approach for monitoring and assessment of growth, development, maturation and nutritional status and can be indicators of a population's health status. The purpose of the study was to determine the body height and body weight of a representative sample of schoolchildren and adolescents from the Tetovo region, and to conduct a comparative analysis of age and gender, and to determine the onset of accelerated growth.

Methods: Sample included 382 schoolchildren and adolescents, 192 boys and 191 girls, aged 12–17 years, in the Tetovo region, North Macedonia. The basic anthropometric measurements (body height and body weight) were taken according to standard protocols of International Biological Program (IBP, Nr.9, 1969).

Results: The mean body height values for boys range from 148.78 cm for those aged 12 to 177.44 cm for those aged 17, and for girls from 146.42 cm for ages 12 to 169.47 cm for those aged 17. The mean body weight values for boys range from 44.23 kg at age 12 to 71.45 kg at age 17, and for girls from 42.05 kg to age 12 to 60.09 kg at age 17.

Conclusion: The analysis of the obtained results suggests that there has been a significant increase in the mean values of Body Height and Body Weight in children and adolescents compared to WHO standards of growth and development.

Keywords: anthropometric measurements; development; growth; schoolchildren; adolescents.

INTRODUCTION

Primary school children and adolescents are the future generation of any country and their nutritional needs are critical for the well-being of society. They are an important segment of population, as they form the first institutionalized group that can be approached for health, nutritional and educational interventions with ease. The rate of growth of children and adolescents varies with the environment in which they live. Today, one of the main tasks of the specialists in Biomedicine disciplines is to combine their efforts to develop and improve the system of assessment and prevention of children and adolescents health [19]. Measuring the anthropometric characteristics in childhood and in adolescence are the most common approach for monitoring and assessment of growth, development, maturation and nutritional status [6], and can be indicators of a population's health status, quality of nutrition and nutritional status, giving rise to increasingly widespread studies of anthropometric characteristics among researchers [2,7,14,28], not only for monitoring children's growth and development, but also for an early detection of overweight and risk of obesity. In the last several decades, obesity has become one of the leading direct and indirect causes of morbidity and mortality in all parts of the world. There is evidence that childhood obesity is widely related to serious health complications and increased early death risk [4]. For an early detection of being overweight in childhood, it is necessary to constantly monitor the growth and development of children and take their anthropometric measurements [1]. Since anthropometric measurements can be indicators of a population's health status,

quality of nutrition and nutritional status, studies of anthropometric characteristics have become increasingly widespread among researchers [2]. In kinesiology research, knowledge of children's anthropological status is required for quality planning and programming of physical activity [5], as well as for the choice of contents that should facilitate growth and development, and which also fall into the category of primary prevention of obesity. The outward signs of growth are the height and weight of children and adolescents. However, the child's height and weight is a good indicator for determining nutritional status. [21]. Anthropometric characteristics including body weight (BW), body height (BH), subcutaneous adipose tissue thickness as well as others, play a significant role in the assessment of growth, development, health status and quality of nutrition. They are also associated with morbidity and mortality [10,11,32]. The physical characteristics of boys and girls begin to change and differ from each other after the infancy period, which is documented in the literature. One of the most significant changes is the sudden increase in BH among boys, shortly before their sexual maturity begins, which begins a year or two later than in girls. Boys grow faster than girls grow into puberty, and continue to grow longer than girls [8,28,30,31]. The school period is an important period from the perspective of the growth and development of children and adolescents. At the beginning of primary school, the constant growth of children continues. Always, according to the literature, the average child growth is about 5-7 cm per year and weight gain is about 2-3 kg, while the body fat percentage decreases. After the age of 10, an average weight gain is about 4-5 kg per year, and new fat accumulations begin in the body. [3,22]. Also, in schoolchildren, changes in body characteristics develop based on gender. At the age of seven, boys are expected to be taller than girls on average about 2-3 cm. The differences in BW are insignificant. On average, at the age of 10, girls are expected to be 1-2 cm taller and 1 kg heavier than boys [22]. The purpose of the study was to determine the body height and body weight of a representative sample of schoolchildren and adolescents from the Tetovo region, and to conduct a comparative analysis of age and gender, and to determine the onset of accelerated growth.

METHODS

Subjects

The study involved 383 schoolchildren and adolescents (192 boys and 191 girls) aged between 12 and 17 years, attending various primary schools and secondary schools in the Tetovo region, North Macedonia. 4 primary schools and 1 secondary school on the territory of the city of Tetovo and surrounding, participated in the study; 22 classes (5 classes from sixth grade, 4 from seventh grade, 3 from eighth grade and 4 from ninth grade in primary schools, and 3 from first grade and 3 from second grade in secondary schools) were randomly selected from each school. The sample consisted of children from 4 schools, i.e. more than 20 % of all primary and secondary schools in the territory of the Tetovo region. The schools and classes were chosen by the random choice method and all the children attending classes at that time underwent measurements.

DATA COLLECTION

The Sample was obtained during a three month data collection, in the period of April 2019 - June 2019.

Measurements

Anthropometric measurements were taken according to standard protocols of International Biological Program (IBP, Nr.9, 1969) [15,26]. Morphological characteristics were assessed using the following anthropometric measurements: Body Height in standing position (expressed in centimeters) was measured, in the standing position to the nearest 0.1 cm using a GPM Anthropometer (GPM Swiss Made Anthropometer) and Body Weight (expressed in kilograms) was measured to the nearest 0.1 kg using an electronic portable scale (Seca 899). To ensure accuracy the scale was checked for zero reading before each weighing and calibrated with a known weight on the morning of each data collection. Participants were weighed and measured in the morning during the physical education class when the subjects were dressed in light clothing and without shoes and socks. The biological age was determined according to the date of birth and date of measurement; for example, children aged from twelve years and six months to thirteen years and five months were included in the age group of thirteen years. All children and adolescents from the study sample were included in their respective age groups accordingly.

ETHICS CONSIDERATION

This study was approved by the Ethics Committee of the Faculty of Medical Sciences, University of Tetovo and carried out according to the Declaration of Helsinki.

The written consent for measuring the children and adolescents was obtained from the Sector for Public Activities - Education Unit in the Muncipiality of Tetova, primary schools and secondary schools Administrations, Board of Management and Principals of primary schools and secondary schools, and council of each school included in the study. Individual contacts were made with school professors.

DATA ANALYSIS

Sample data were analyzed using SPSS Version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). The statistical analysis included the following descriptive statistical parameters: mean value, standard deviation, minimum and maximum of all values, coefficient of variation (CV) and confidence interval. The following multivariate and univariate procedures were applied: Student's t-test, multivariate analysis of variance (MANOVA), univariate analysis of variance (ANOVA).

RESULTS

Tables 1–4 show the basic anthropometric characteristics measured separately for boys and girls.

Body height

Boys

The average values of BH for the boys sample ranged from 148.78 cm in those aged 12 years to 177.48 cm in those aged 17 years (Table 1). CV values suggest the homogeneity in all age groups among boys. Increased skewness values of BH in boys indicate that the distribution was negatively asymmetrical, meaning that the result distribution curve skewed to the higher values, i.e. higher values prevailed in relation to normal distribution in age groups from 12 to 14 years. The decreased skewness values indicate that the distribution was positively asymmetrical, meaning that the result distribution curve skewed to the lower values, i.e. lower values prevailed in relation to normal distribution in age groups of 16 and 17 years. The skewness values indicate that the distribution was symmetrical in boys aged 15 years. Higher values of kurtosis indicate that the curve was peak in the age groups of 12, 14, 16, and 17 years. The negative kurtosis values indicate that the curve was flat in boys aged 13 and 15 years. The distribution of BH values of boys ranged mostly within normal distribution (p) in boys aged 17 years. The distribution of values deviated from the normal distribution (p) in other age groups of boys, i.e. in those 12 to 16 years old.

Table 1. Body height (cm) in the boys sample

Age	N	Mean	SD	SE	Min	Max	CV	CI		Skew.	Kurt.	p
12	31	148.78	6.78	0.23	133.8	174.9	4.77	148.30	149.26	0.21	0.16	0.000
13	33	154.62	7.46	0.24	135.4	181.9	4.79	154.11	155.14	0.03	-0.14	0.000
14	32	161.25	7.53	0.31	139.7	189.9	5.67	160.66	161.84	-0.33	1.06	0.000
15	31	164.94	8.47	0.33	144.2	191.8	5.75	164.27	165.61	-0.11	1.01	0.636
16	34	169.94	8.86	0.36	146.1	194.6	5.31	169.20	170.67	0.17	0.19	0.000
17	31	177.48	8.38	0.76	147.6	195.3	4.59	176.28	178.69	0.23	0.22	0.000

N - number; SD - standard deviation; SE - standard error; Min. - minimum; Max. - maximum; CV - coefficient of variation; CI - confidence interval; Skew. - Skewness; Kurt. - Kurtosis

Girls

Average values of BH for the sample of girls attending primary schools and secondary schools in the Tetovo region ranged from 146.42 cm in those aged 12 years to 169.47 cm in those aged 17 (Table 2). CV values suggest the homogeneity in all age groups among girls. Analyzing BH in girls, the increased skewness values indicate that the distribution was negatively asymmetrical, meaning that the result distribution curve skewed to higher values, i.e. higher values prevailed in relation to normal distribution in ages 13 and 17 years. Skewness values indicate that the distribution was symmetrical for the ages of 12 and 14. The decreased skewness values indicate that the distribution was positively asymmetrical, meaning that the result distribution curve skewed to lower values, i.e. lower values prevailed in relation to normal distribution in 15 and 16 year old girls. Higher values of kurtosis indicate that the curve was peak in the age groups of 14, 15, 16 and 17 years, and negative kurtosis values indicate that the curve was flat in girls aged 12. In the analyzed group of girls, the distribution of BH values ranged mostly within normal distribution (p) in age groups of 17 years, and deviated from normal distribution (p) in other age groups of girls, i.e. in those 12 to 16 years old.

Table 2. Body height (cm) in the girls sample

Age	N	Mean	SD	SE	Min	Max	CV	CI		Skew.	Kurt.	p
12	30	146.42	7.34	0.25	129.8	164.3	4.07	145.33	147.51	0.00	-0.19	0.000
13	32	153.01	7.75	0.27	129.6	177.9	5.15	152.31	153.72	0.07	0.00	0.000
14	34	159.71	6.63	0.29	135.7	185.8	4.91	158.69	160.73	-0.67	3.76	0.000
15	31	163.18	6.95	0.26	142.4	185.3	4.28	162.84	163.53	0.16	0.08	0.943
16	33	166.45	6.91	0.28	146.9	186.5	4.15	165.95	166.96	0.17	0.07	0.000
17	31	169.47	7.37	0.73	149.3	190.4	4.37	168.44	170.50	0.18	0.10	0.000

N - number; SD - standard deviation; SE - standard error; Min. - minimum; Max. - maximum; CV - coefficient of variation; CI - confidence interval; Skew. - Skewness; Kurt. - Kurtosis

Body weight

Boys

Average values of BW for the boys sample ranged from 44.23 kg in the youngest group of schoolchildren, aged 12 years old, to 71.45 kg in the adolescents, aged 17 years (Table 3). CV values suggest the homogeneity in 17 year old boys, and higher values indicate the homogeneity in the age group from 12 to 16 years. Skewness values of BW were increased, indicating that the distribution was negatively asymmetrical. This means that the result distribution curve skewed to the higher values, i.e. higher values prevailed in relation to normal distribution in all age groups among boys. Higher values of kurtosis indicate that the curve was peak in the age groups 16 and 17 years and negative values indicate that the curve was flat in boys aged 12 to 15 years. According to measured BW values in boys, the distribu tion of values ranged mostly within normal distribution (p) for 17 year old boys, and deviated from the normal distribution (p) in other analyzed age groups.

Table 3. Body weight (kg) in the boys sample

Age	N	Mean	SD	SE	Min	Max	CV	CI		Skew.	Kurt.	p
12	31	44.23	8.35	0.34	23.5	66.3	21.83	43.64	44.83	1.53	-0.27	0.000
13	33	48.74	9.27	0.32	27.9	72.2	21.25	48.09	49.39	1.51	-0.34	0.000
14	32	53.62	11.31	0.39	28.6	80.3	23.43	52.83	54.41	2.57	4.48	0.000
15	31	58.52	11.29	0.43	31.1	87.6	22.37	57.65	59.40	0.43	1.05	0.135
16	34	63.66	12.65	0.47	24.7	104.4	19.33	62.69	64.63	0.27	0.18	0.000
17	31	71.45	10.62	1.17	39.8	103.7	17.58	69.10	73.80	0.23	0.15	0.000

N - number; SD - standard deviation; SE - standard error; Min. - minimum; Max. - maximum; CV - coefficient of variation; CI - confidence interval; Skew. - Skewness; Kurt. - Kurtosis

Girls

The average values of BW for the girls sample ranged from 42.05 kg in the youngest age group of schoolchildren, aged 12 years old, to 60.09 kg in the oldest girls, aged 17 years (Table 4). CV values suggest the homogeneity in girls aged 15, 16 and 17 years, and higher values indicate the homogeneity in the age group from 12 to 14 years. Analyzing BW in girls, skewness values were increased, indicating that distribution was negatively asymmetrical. That means that result distribution curve skewed to higher values, i.e. higher values prevailed in relation to normal distribution in all age groups among girls. Higher values of kurtosis indicate that the curve was peak in the age groups 12, 16 and 17 years, and negative values indicate that the curve was flat in 13 and 14 year old girls. The distribution of BW values in the group of analyzed girls ranged mostly within normal distribution (p) in girls aged 17 years. The distribution of values deviated from normal distribution (p) in other age groups of girls.

Table 4. Body weight (kg) in the girls sample

Age	N	Mean	SD	SE	Min	Max	CV	CI		Skew.	Kurt.	p
12	30	42.05	9.33	0.31	23.7	81.5	22.18	41.41	42.70	1.64	-0.18	0.000
13	32	46.52	9.87	0.35	24.3	84.7	20.78	45.83	47.21	1.71	0.02	0.001
14	34	51.72	9.95	0.36	26.7	100.2	19.31	51.03	52.41	2.75	5.14	0.001
15	31	53.99	9.37	0.94	34.5	91.4	17.22	52.55	55.43	1.07	2.76	0.639
16	33	56.66	9.94	0.39	29.8	102.0	19.30	55.64	57.69	1.25	0.14	0.000
17	31	60.09	9.38	0.95	38.6	92.1	17.17	58.01	62.18	1.39	0.08	0.000

N - number; SD - standard deviation; SE - standard error; Min. - minimum; Max. - maximum; CV - coefficient of variation; CI - confidence interval; Skew. - Skewness; Kurt. - Kurtosis

DISCUSSION

The aim of this study was to determine the BH and BW by age and sex, and examine the sex differences in anthropometric characteristics among schoolchildren and adolescents in the Tetovo region. By analyzing BH results obtained for boys from our study sample in relation to results of other studies performed worldwide, it can be noticed that the BH values found in boys from Tetovo region were higher compared to WHO standards of growth and development, and similar to some previous studies conducted in the region and the world [9,17]. Comparing the mean body weight values of the girls included in this study with the results of similar international and national studies, it can be concluded that that the BH values found in girls from Tetovo region were higher compared to WHO standards of growth and development, and had mean BH values approximate to their peers included in other similar studies. [9,16,17,18,23]. In addition to the BH analyzes, BW in this study was analyzed as a very important anthropometric parameter, which is one of the main representatives of children's nutritional status, and is often determined by environmental factors and lifestyle rather than BH. Comparing the BW results of the girls included in our study and the results obtained in other similar studies we can see that the mean BW values in the younger age group from this study sample were lower only in relation to their peers from neighboring countries. But, however, when we compare the mean BW values recorded in the oldest age groups of girls in all studies, we can see that these values were higher among girls from Tetovo only to some studies of girls from India, who could be due to genetic predispositions [9,16,17,18,23]. As long as the BW parameter is in a close correlation with the background, habits, lifestyle [20,24], we can assume that the differences we found in the mean BW values, with respect to boys and girls from other studies can be attributed to these factors. By analyzing the morphological and anthropometric characteristics by age group of schoolchildren and adolescents aged 12 to 17 in the Tetovo region, the authors found differences across all age groups in the ratio of BW and BH in the majority of boys sample, specifically boys of age from 13 to 16 years, which suggests that higher rising is in these parameters. The highest increase in these two parameters was observed in girls aged from 14 years, while girls 16 and 17 years had similar values for these two parameters. The results of this study are consistent with the data found in the literature. Adolescence is the period of sudden development and growth, in which girls usually enter after the age of 10, while boys enter adolescence on average two years later than girls. [12,25].

Limitations

The limitation of the study is that it is ''cross-sectional'' study. It would be of greater scientific importance a ''longitudinal'' study, to monitor for an extended period of time the anthropometric characteristics of schoolchildren and adolescents, which would give us a more accurate picture about their growth and development.

CONCLUSION

The analysis of the obtained results suggests that there has been a significant increase in the mean values of BH and BW in children and adolescents compared to WHO standards of growth and development. Although this study was conducted on a small proportion of schoolchildren and adolescents in the Tetovo region, we have clearly seen the high prevalence of overweight and obesity in many individuals during the measurement. This information above can help target high risk individuals. However, further studies with a larger sample of schoolchildren and adolescents will provide a more accurate picture of the overweight epidemic in schoolchildren and adolescents in the Tetovo region. Our results underline the need to plan preventive and remedial strategies aimed at reducing

weight in schoolchildren and adolescents and thereby limiting associated risk factors. Nutritional intervention programs should be conducted at school, including students' parents and their medical doctors, and should be taught by trained teachers using the most appropriate communication techniques. Some intervention efficacy indices will be selected and analyzed, such as dietary habits and consumption, level of physical activity, body weight loss, and positive changes in other risk factors. Many studies in various disciplines (medicine, sociology, psychology and economics) have highlighted how overweight and obesity are a significant issue not only in terms of physical and mental health but also with regard to their huge economic and social impact. For this reason, different governments and the WHO promote overweight and obesity prevention programmes during childhood and adolescence, when it is easier to modify lifestyles compared with adulthood. Such programmes usually suggest strategies to favour a correct diet and adequate exercise [13].

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FOOTNOTES

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Conflict of interests:

The authors declare no conflict of interests.

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Review

TERAPI ME PRP (PLATELETS RICH PLASMA / PRP)

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ABSTRAKT

Terapi me PRP është një metodë revolucionare që përdororet në një mënyrë krejtësisht të natyrshme për shërim të shpejtë dhe regjenerimin pas lëndimit të indeve dhe inflamacion në nyje, muskuj, tendina si dhe ligamente. Mundet të përdororet shpesh në regjenerimin e meniskut dhe kërcit në nyje, në mënyrë që të shmangen procedurat kirurgjikale.

Artrosat, lëndime të tendoniave, ligamenteve dhe muskujsh, si dhe sindroma dhimbjes kronike janë shpesh një problem serioz për pacientët dhe punëtorët shëndetësor në ortopedi, traumatologji, fizioterapi dhe mjekësisë sportive. Rezultati i këtyre gjendjeve është zvogëlimi I kapacitetit të punës gjatë kohë, ose mungesa e gjatë nga fusha e sportit .

Përveç regjenerimin e indeve, kjo metodë ka një efekt pozitiv mbi gjendjen e përgjithshme të trupit dhe bën më të lehtë dhe të mundur lëvizjen pa dhimbje. aplikim të veçantë dhe rezultate të shkëlqyera terapia me PRP ka në arthrosis, coxarthrosis, ndryshimet degjenerative në nyje supe, bërryla, kërlokun, gjunjë, nyje të këmbës, etj, për të përmirësuar drejtpërdrejt shërimin dhe rigjenerimin e indeve, të tilla si menisket, kërci i kyçeve dhe të parandaluar përkeqësimin e saj.

Terapia PRP gjithashtu përshpejton shërimin pas operacionit në tendina dhe ligamente, muskujt dhe nyje.

Terapi PRP mundet të përdororet edhe në mjekësi estetike si një trajtim për fytyrë dhe pjesë të tjera të trupit, ku ne duam të nxisim regjenrim

ÇFARË ËSHTË TERAPIA PRP?

PRP (Platelets Rich Plasma / PRP) është pjesë e plazmës së gjakut e pasur me trombocitet, të cilat përmbajnë faktorët e rritjes dhe substancave të tjera që marrin pjesë në mënyrë aktive në shërimin dhe regjenerimin e indeve të dëmtuara dhe të sëmurë, apo në trajtimin estetik.

Duke përdorur gjakun e pacientit, me metoda të veçanta për të bërë pasurimin e plazmës me trombocitet që më pas injektohet në zonën e dëshiruar që ne duam për të trajtuar.

Pas injekimit të PRP bëhet lirimi i substancave nga trombocitet (faktorëve të rritjes) që të nxitur shërimin dhe regjenerimin. Përqendrimi trombociteve rrit sasinë e substancave që nxisin procesin e shërimit. Trupi i njeriut ka një fuqi të mahnitshme dhe të shërueshme duke përdorur trombocitet në masë të madhe ndihmojnë dhe përshpejtojnë procesin e shërimit.

KU ËSHTË E APLIKUESHME TERAPI ME PRP?

Terapi PRP është aplikuar në situatën në të cilën ne duam të inkurajojmë shërim më të shpejtë dhe trajtimin e indeve. Në rast të dëmtimit të sistemit muskuloskeletor (lëndime të muskujve, ligamente, tendonave ...), ndryshimet degjenerative në nyje (kërllok, gjunjë, shpatull ...) në trajtimin e plagëve kronike, mjekësisë estetike etj.

SI APLIKOHET TERAPIA ME PRP?

Pacientit i merret një sasi të caktuar të gjakut të plotë nga ena e gjakut, më pas bëhet një trajtuim me një metodë të veçantë e nku fitohet plazmma me numritë zmadhuar të trombociteve. Produkti që rezulton infiltrohet me injeksion në pjesën e para-përcaktuar të pacientit. E

gjithë procedura zgjat 15-30 minuta.

I përket një ndërhyrjet shumë të sigurt. I vetmi shqetësim që pacienti mund të ketë janë tipike për të dhënë ndonjë lloj të injektimit (dhimbje, gjakderdhje, skuqje në vendin e injektimit).

ZBATIMI I PRP KA PËRPARËSITË E MËPOSHTME:

Të shpejë dhe të lehtë për t'u përdorur - Ajo merr vetëm disa hapa për të nxjerrë 4-5 ml PRP

I sigurtë - gjaku i pacientit është përdorur dhe kështu shmang rrezikun e infektimit me HIV dhe sëmundjeve të tjera infektive.

Nje sasi e vogël e gjakut - kërkohet një sasi të vogël të gjakut

Si mjekohet dhimbja pas trajtimit me PRP?

Përdorni qetësues, ju lutem të përshkruara vetëm. Trajtimi lokal varet nga zona dhe llojit të trajtimit (lëndimet sportive, sëmundjet, procedurat estetike, etj).

Mos përdorni barrëra jo-steroide anti-inflamatore (Brufen, ibuprofen, naproxen, ketone, etj).

Kur terapi PRP nuk zbatohet?

Ka kontraindikacione absolute dhe relative e trajtimit me PRP. Në kontraindikacione absolute kur trajtimi nuk mund të zbatohen përfshijnë:

Sëmundjet malinje

Çrregullimet sistemike të gjakut

Gjendje akute infective

Në kontraindikacione relative kur përgatitjen e duhur të një pacienti mund të kryejnë trajtim përfshijnë:

Sëmundjet autoimune e kockave dhe sistemit të nyjeve

Sëmundje kronike të mëlçisë dhe të veshkave

Intervenime kirurgjike në 30 ditët e fundit

Pacientët me kuagulopati

Administrimi i kortikosteroideve 4-6 javë para ndërhyrjes

Përdorimi i barrërave jo-steroid anti-inflamatore në 7 ditet e fundit

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„УЛОГАТА НА ГЕНИТЕ TOB1, HMGA1, COX-2 И FLNA ВО КОЛОРЕКТАЛНАТА КАРЦИНОГЕНЕЗА“

д-р Бујар Османи

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АПСТРАКТ

Кус вовед: Колоректалниот карцином е мошне честа и хетерогена група на неопластични заболувања чија анатомска локализација, потенцијал за прогресија, одговор кон третманот и прогнозата, значително се разликуваат во зависност од молекуларно-генетските абнормалности и нивната карактеристична комбинација во малигните клетки.

Цели: Целт на овој ревијален труд да се направи преглед на литературата за улогата на гените: TOB1, HMGA1, COX-2 и FLNA во колоректалната карциногенеза како и досега утврдената корелација помеѓу експресијата на овие гени од една страна, и основните клиничко-патолошки параметри: градусот, стадиумот, локалната распространетост и присуството на оддалечени метастази според TNM класификацијата, како и анатомската локализација на туморот (десен, лев хемиколон или ректум) од друга страна.

Клучни зборови: колоректален карцином, молекуларно-генетска студија, TOB1, HMGA1, COX-2 и FLNA гени

ВОВЕД

Колоректалниот карцином (КРК) претставува малиген тумор кој потекнува од епителните клетки на колонот и/или ректумот. КРК е најчесто малигно заболување на гастроинтестиналниот тракт со мултифакторијална етиологија каде што генетската основа, факторите на околината и/или инфлматорните заболувања на цревото доведуваат до малигна трансформација на нормалниот епител на слузницата на колонот и/или ректумот преку неколкугодишен етапен процес на акумулација на генетски и епигенетски алтерации.

Веќе 25 години е познато дека малигната трансформација и постепената прогресија на промените од нормалниот епител на дебелото црево, преку аденомот, карциномот in situ, па сè до инвазивниот карцином, е проследена со последователна низа на молекуларно-генетски нарушувања (1). Резултатите од исклучително големиот број на спроведени студии утврдиле голем број на поединечни молекуларни абнормалности какви што се: генските мутации, промените на нивоата на генската експресија, единечните нуклеотидни полиморфизми (SNP), DNA-метилацијата, геномската нестабилност, хромозомски аберации, како и други промени (2). Сите овие молекуларно-генетски и епигенетски нарушувања имаат клучна улога, не само врз самиот процес на малигна трансформација на епителот на колонот, туку и врз вродената предиспозиција, приемчивоста кон оваа неоплазма, текот на болеста и терапевтскиот одговор. Канонскиот модел на колеректална малигна трансформација се базира на секвенционално, постепено акумулирање на генски мутации како и епигенетски промени кои афектираат неколку клучни други онкогени, тумор-супресорски и други гени, вклучувајќи ги APC, RAS, BRAF, TP53, TGF-з, PI3KCA, SMAD4, групата гени MMR, MYH, EPCAM MMP, MSX, ЕПЦАМ и други (3).

Досега се направени повеќе обиди за класификација на карциномите на колоректумот, базирана на молекуларните и генетските разлики. Според една од нив, најчестиот тип кој е присутен кај 60-70 % од сите случаи на спорадичен колоректален карцином е карактеристичен по хромозомската нестабилност (CIN) и разни хромозомски нумерички аберации и анеуплоидии, како и со мутации во определени гени, од кои најистражени се: APC, KRAS, PIK3CA, BRAF, SMAD4, TP53 и други (4). Според истата класификација, вториот тип е застапен кај 10-15 % од сите случаи на спорадичен карцином и е карактеристичен по геномската нестабилност. Овој тип најчесто се детектира по микростаелитната нестабилност (MIN) предизвикана од дисфункција на гените задолжени

за репарација на мутациите. Третиот тип се наоѓа кај приближно 5 % од сите спорадични случаи и е карактеристичен по обемната метилација на CpG островчињата лоцирани во генските промотори што ја потиснува експресијата на афектираните гени (5). Останатите случаи имаат определеана комбинација или, пак, немаат ниту една од овие три молекуларни и генетски карактеристики.

Со напредни статистички анализи на податоците од голем број молекуларно-генетски и патолошки студии, неодамна е претпоставено дека постојат четири основни консензусни молекуларни субтипови (CMS) на колоректален карцином: CMS1 (хипермутаторен фенотип со микросателитна нестабилност и силна имунолошка активација); CMS2 (канонски епителен тип, нагласена активација на сигналните патишта WNT и MYC); CMS3 (метаболички тип со јасна епителна и метаболна дерегулација) и CMS4 (месенхимален тип со проминентна активација на TGF-3, со нагласена стромална инвазија и ангиогенеза (6).

Досегашните студии недвосмислено укажуваат на фактот дека спорадичниот колоректален карцином е хетерогена група на заболувања на дебелото црево. Оттаму, иако хистолошки идентични, овие неоплазми можат сигнификантно да се разликуваат според молекуларниот профил на генските нарушувања. Сепак, метастудиите утврдиле дека молекуларно-генетските промени функционално афектираат релативно мал број интрацелуларни патишта задолжени за регулацијата на критичните клеточни процеси: делбата, апоптозата, клеточната инвазија на околното ткиво, мобилноста на клетките и други карактеристики релевантни за малигнитетот .Се смета дека доминантниот клон на малигни клетки кој преовладува во туморската маса содржи уникатна комбинација на молекуларни нарушувања и ги детерминира, барем во временскиот период во кој е доминантен, биолошките карактеристики на неоплазмата, односно клиничкиот тек, терапевтскиот одговор и прогнозата на болеста кај пациентот.

Од хируршки аспект, мошне е интересно што неколку студии спроведени во текот на последниве години индицираат дека колоректалниот карцином е хетероген и по однос на локацијата на туморот. Имено, како што произлегува и од ембриолошките и анатомските истражувања, десниот-проксимален дел од колонот кој се протега сè до спленичната флексура и левиот-дистален дел од флексурата до ректумот се всушност два различни ентитети. Утврдено е дека молекуларно-генетските промени во голема мерка се разликуваат меѓу овие два дела на дебелото црево (7,8). Микросателитната нестабилност и нарушувањата на функцијата на гените вклучени во репарацијата на мутациите доминираат во проксималниот дел од колонот, додека хромозомските абреации и мутациите во определени гени се почести кај карциномите во дисталниот дел од колонот и ректумот. Овие две големи групи на молекуларни абнормалности содржат голем број на поединечни мутации и нарушувања на нивоата на експресија на определени гени. Понатаму, најдена е и поврзаност на ваквите разлики со клиничкиот исход, односно прогнозата на болеста.

Одговорот кон адјувантната хемотерапија и, во поново време, кон таргетираната терапија, пред сè со моноклонални антитела, исто така значајно варираат врз основа на овие анатомски разлики и молекуларните абнормалности кај колоректалниот карцином, Во некои студии, опишано е дека адјувантната терапија со 5-флуороурацил има поволен клинички одговор само кај пациентите чии тумори содржеле промени од групата на хромозомските аберации и генски мутации кои најчесто ги придружуваат, додека терапискиот ефект, не само што отсуствувал, туку и го скусувал преживувањето кај пациентите кај кои биле најдени промените од групата на микростаелитна нестабилност (9). Оттаму произлегува дека ваквите студии немаат само академски карактер и резултати важни за базичната биологија на неоплазмите, туку можат да имаат и практична примена во текот на клиничкото носење на одлуки околу обемот и изборот на хируршкиот, зрачниот, хемотерапевтскиот и адјувантниот третман (10).

Иако досега се објавени енормен број на податоци за генските абнормалности кај колоректалниот карцином, се смета дека оваа интердисциплинарна биомедицинска област е сè уште во рана фаза од развојот, па постојат уште голем број на неодговорени прашања и неоткриени корелации меѓу промените и клиничките аспекти на ова заболување.

Покрај наведените испитувани гени кај KRK, во последниве години се вршат анализи и на голем број други гени кои се поврзани со определени клинички и патолошки карактеристики на оваа неоплазма и кои се помалку проучни, но, потенцијално релевантни од апликативен и од научен аспект. Меѓу нив, во оваа студија од интерес се гените: TOB1, HMGA1, COX-2 и

FLNA.

Генот TOB1 е член на фамилија Tob/BTG гени кои кодираат антипролиферативни протеини вклучени во регулацијата на клеточниот циклус. Поновите истражувања индицираат дека TOB1 е кандидатен тумор-супресорски ген лоциран на хромозомскиот локус 17q21, чиј протеински продукт е сигнален трансдуктор на erbB-2 рецепторната тирозин-протеинска киназа, а влегува и во меѓупротеински интеракции со низа пролиферативни протеински молекули, делувајќи инхибиторно на нив, а со тоа попречувајќи ја прогресијата на клеточниот циклус и запирајќи го во G0/G1 точката на транзиција (11). Покрај тоа, експериментите утврдиле и дека лабораториските глувци кои имаат нефункционален ген TOB имаат висока инциденција на спонтани тумори.

Мал број истражувања на експресиските нивоа на генот се направени досега кај хепатоцелуларните, тироидните и карциномите на дојка (12). Спротивно на тоа, опишано е дека кај колоректалните карциноми, експресијата на TOB1 генот е зголемена во однос на немалигните ткива и дека нивоата на генска експресија сигнификантно корелираат со клиничко-патолошкиот стадиум на болеста, а прекумерната експресија статистички значајно корелира со метастазите во лимфните јазли (13).

Генот HMGA1 (кратенка од англ.: high-mobility group A1 proteins) е лоциран на хромозомскиот локус 6p21 и кодира нехистонски хроматински протеин инволвиран во транскрипциската регулација на генската експресија, DNA-репликацијата, хетерохроматинската организација и други клучни процеси во клетката. Недиференцираните ембрионални и трансформираните клетки имаат високи нивоа на експресија на генот HMGA1, додека таа е ниска или целосно отсуствува кај диференцираните соматски клетки што укажува на клучната улога на овој ген во регулирањето на клеточниот раст и пролиферација (14). Во поново време, најдена е абнормално висока експресија на генот HMGA1 кај некои малигни неоплазми, вклучувајќи го и колоректалниот карцином (15). Во релативно ретките студии кај оваа неоплазма, идентификувана е и корелација на високата експресија на генот HMGA1 со потенцијалот за метастазирање во локалните лимфни јазли и хематогеното дисеминирање, како и со лошата прогноза на болеста (16).

Генот COX-2 (официјално ознаен како PTGS2) се наоѓа во хромозомскиот локус 1q25.2-q25.3 и кодира ензим со клучна улога во синтезата на простагландините и тромбоксаните, кои ги стимулираат инфламацијата, клеточната пролиферација и ангиогенезата. Сите овие процеси имаат важна улога во патогенезата на колоректалниот карцином (17). Повеќе истражувања укажале на тоа дека прекумерната експресија на COX-2 генот е многу често застапена кај околу 80% од пациентите, како и дека е поврзана со значително полоша прогноза и повисока веројатност од метастазирање на колоректалниот карцином (18,19). Анатомската диспропорционалност е забележана и кај овој параметар, па во една од студиите најдено е дека експресијата на COX-2 генот е абнормално зголемена кај 70% од карциномите на левиот, наспроти кај 46% од десниот колон

Четвртиот ген кој е предложен за испитување е FLNA генот лоциран на хромозомот Xq28, кој го кодира протеинот Filamin A, и е вклучен во реорганизацијата на актинскиот цитоскелет во клетката (20). Прекумерната експресија на овој протеин, под определени услови, меѓу кои и исклучиво цитоплазматичното акумиулирање, е најдена кај некои типови на малигни неоплазми, но се чини дека нивоата, тајмингот, траењето и диструбицијата на протеинскиот продукт влијаат врз стимулирачкиот или инхибиторниот ефект врз клеточната пролиферација (21). Досега е објавена само една студија, и тоа во февруари 2015 година, во која се детектирани намалени новоа на експресија на генот FLNA кај колоректалниот карцином (22).

Истражувањата на молекуларно-генетските нарушувања кај колоректалниот карцином се спроведуваат веќе неколку децении, но претежно се насочени само кон десетина гени или генетски и молекуларни нарушувања.

Досега објавените студии за експресијата на генот COX-2 се контрадикторни, па неговата квантитативна детекција кај македонската популација пациенти може да има научен придонес во расветлувањето на поврзаноста со испитуваните клиничко-патолошки параметри. Покрај тоа што се многу малку истражувани во светски рамки, слично се однесува и на гените TOB1 и HMGA1. Генот FLNA е исклучително малку проучен кај колоректалниот карцином и е вистински предизвик за оригинално истражување во популацијата на наши пациенти со оваа неоплазма.

Покрај научната перспектива, посебен предизвик е и хируршката сигнификантност на потенцијалната поврзаност на некои од генските параметри со анатомската локализација на туморот, како и перспективната употребливост на сознанијата за молекуларна субтипизација, клиничко-патолошка проценка, предвидување на текот на болеста и други практични примени.

Покрај тоа, во достапната литература постои значителна дискрепанца во однос на фреквенцијата и клиничката сигнификантност на абнормалната експресија на генот COX-2. Покрај тоа, исклучително мал број студии досега се извршени за улогата на гените TOB1, HMGA1 и FLNA во патогенезата на колоректалниот карцином, со што е реалистично да се очекува оригинално идентификување и квантитативно опредеување на корелациите на нивните експресиски нарушувања со клиничко-патолошките параметри, а кои можат да отстапуваат од досега ретките објавени трудови.

Со оглед на актуелноста на темата, како и уникатната комбинација на овие четири гени која досега не е објавена во ниту една студија, се очекува изработка на квалитетна, современа, оригинална и публикабилна докторска студија.

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НЕЗАДОВОЛЕНИ МЕДИЦИНСКИ ПОТРЕБИ КАЈ ПАЦИЕНТИТЕ СО СПИНАЛНА МУСКУЛНА АТРОФИЈА: РЕВИЈАЛЕН ТРУД

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АПСТРАКТ

Авторите ценат дека овој ревијален труд (преглед на достапна стручна литература) е од есенцијално значење како за пациентите така и за медицинските лица бидејќи досега многу малку се пишувало и истражувало за спиналната мускулна атрофија (СМА). Се обидовме одблиску да ја отсликаме моменталната состојба во која се наоѓаат пациентите со СМА во светски рамки. На тој начин ќе укажаме и на предизвиците и на недостатоците во односот меѓу медицинските лица и овие пациенти, со цел поттикнување на превземање на соодветни мерки кои ќе водат кон подобрување на квалитетот на нивниот живот. Нашата визија е оваа творба да биде зачеток на многу интересни истражувања во блиска иднина, во корист на пациентите како и за надоградба на знаењата на медицинскиот персонал во однос на СМА.

Клучни зборови: спинална мускулна атрофија, СМА, пациенти, незадоволени, медицински потреби

ЗА СПИНАЛНА МУСКУЛНА АТРОФИЈА

Спинална мускулна атрофија (СМА) е ретка, автозомно рецесивна, генетска болест. СМА има широк опсег на сериозност и нејзината преваленца варира од регион до регион. Вкупната инциденца на СМА за сите фенотипови, кај сите етнички групи изнесува 1 на 11.000 живородени деца [1]. СМА генерално се карактеризира со прогресивен губиток на нервните сигнали во мускулите, намалување на мускулната маса (скелетна мускулна атрофија), целокупна слабост, губиток на постигнатата моторна функција итн. Мускулната атрофија води до компликации поврзани со болеста кои можат да влијаат врз преживувањето: искривување на ‘рбетниот столб (сколиоза), повторувачки епизоди на пневмонија, тешкотии со спиење и исхрана, потреба од респираторна, нутритивна, ортопедска и поддршка при одење. Овие компликации водат кон губиток на квалитетот на живот [2, 3, 4, 5].

Етиологија и класификација

СМА се јавува како резултат на дефицит на SMN протеинот и типот се одредува според возраста кога се појавува и максималната постигната моторна функција. Претставува автозомно рецесивна болест што значи дека се јавува како последица на мутација или делеција на две копии на генот за преживување на моторниот неврон 1 (анг. survival motor neuron 1, SMN1) [6]. Ова резултира со недоволни нивоа на SMN протеинот насекаде низ телото, кој директно влијае врз клетките и ткивата во периферијата. Од друга страна пак бројот на копии на SMN2 генот варира од 1 до 6 примероци кај пациентите со СМА, со инверзна врска забележана помеѓу типот на СМА и бројот на копии на SMN2 генот. [5].

Откритија во последните две децении од истражувањата спроведени кај спинална мускулна атрофија

Во 1891 година за првпат е опишан пациент со СМА од страна на Werdnig. Во 1991 година направена е класификација на спиналната мускулна атрофија во три главни типови. 1995 година е од големо значење, бидејќи откриен е SMN1 генот. Во 2010 година започна првата пре-клиничка студија која ја истражува

SMN1 генската терапија. Во 2016 година за првпат се изведуваат студии со risdiplam кај лица со СМА. Истата година, ФДА (анг. Food and Drug Administration) го одобри nusinersen за клиничка употреба како прв одобрен лек за СМА. Благодарение на овој напредок, 2016 година се смета за револуционерна година кога е во прашање третманот на пациентите со спинална мускулна атрофија. Во 2018 година се обновени стандардите за грижа со препораки за СМА, а во 2019 година ФДА го одобри onasemnogene abeparvovec (генска терапија). Се очекува оваа година, risdiplam да биде одобрен за клиничка употреба кај широка група на пациенти со СМА како прв орален, системски SMN2 модификатор за врзување [6, 7, 8, 9, 10, 11].

СМА товар за пациентите и за нивните семјества

Негата и поддршката од семејството е основен дел од управувањето со СМА, но ова може да биде неверојатно тешка задача како за родителите, така и за негувателите. Најчестите предизвици со кои се соочуваат се следниве: [12, 13, 14, 15]

Следење на растот на детето и идентификување на проблемите со хранење или варење [13]

План за медицински итни случаи, покрај следењето на потребите за секојдневна грижа [13, 14]

Прилагодување на семејниот дом за да биде достапен за пациентот [14]

Следење на респираторната функција на детето и одржување на непречен проток на воздух [13, 14]

Чести потешкотии со центрите за медицинска (здравствена) грижа

Голем дел од пациентите со СМА, преминот од медицинската грижа за деца во медицинската грижа за возрасни го опишуваат како искуство кое истовремено претставува предизвик и страв од непознатото. Овие тешкотии во најголем дел се однесуваат во прилагодувањето на учењето нови вештини за навикнување во нов и покомплексен систем на медицинска грижа (се мисли на системот за медицинска грижа на возрасните пациенти), како и на специјалистите кои ги запознаваат, чиј пристап го опшуваат како „поладен" од претходниот. Скоро сите пациенти имаат тешкотии во идентификацијата и пристапот кон специјалистите кои работат во мултидисциплинарни клиники за возрасни пациенти со СМА. Пациентите исто така опишуваат и потешкотии во пристапот кон финансирање и обезбедување на опрема која притоа им е неопходна, како и постоење на јаз во обезбедувањето на информации за подршка и полесен начин за акомодација во околината. Главно се прикажани незадоволствата од недостатокот на асистенти за поддршка, како и на упатства за полесно обострано разбирање на околината. Мноштво од пациентите изразуваат желба за постоење на мултидисциплинарни здравствени установи каде главен фокус ќе биде спиналната мускулна атрофија. Преферираат холистички пристап каде во центарот на вниманието ќе биде пациентот. Ваквиот вид на здравствени установи би бил од голема полза бидејќи ќе има полесен пристап за клинички и терапевтски истражувања. Барањето за ваков вид на медицински установи произлегува од потребата дека полесно ќе се разберат нивните незадоволени медицински барања, а како резултат на тоа побрзо и поадекватно ќе се одговори на истите [15].

Перцепција на ангажманот на центрите за здравствена грижа и нивното влијание

Несоодветниот ангажман на центрите за медицинска грижа доведува до големи разочарувања кај пациентите. Искуствата во вид на кратки и површни интеракции со незаинтересирани или неквалификувани медицински лица, како и ограниченият пристап до поддршка создаваат перцепција дека не се доволно ценети и третирани од страна на здравствениот систем. Дел од пациентите се откажуваат од препорачаното следење (follow up) на текот на болеста после само една средба со системот за здравствена заштита на возрасните пациенти. Пациентите сметаат дека тоа е залудно трошење време и дека им е потребно повиско ниво на самозаштита. Варијациите во текот на болеста исто така играат голема улога во следењето на болеста. Пациентите со постабилни симптоми и полесен фенотип се откажуваат од овој процес. Сметаат дека болеста повеќе им претставувала функционален проблем, без промени во текот на годините, па така не чувствуваат потреба од препорачаното следење на болеста. Спротивно на тоа, напредувањето на болеста и функционалното влошување е причина возрасните пациенти со СМА повторно да ја преиспитаат потенцијалната вредност на здравствената заштита и активно да бараат здравствени услуги.

Можноста за пристап до нови третмани, како што е nusinersen (првата одобрена терапевтска опција за СМА) претставува мотивационен момент од големи

размери за пациентите и нивно повторно вклучување во системот за здравствена заштита.

Зависноста на секојдневниот живот од центрите за инвалидитети и поддршката од заедницата

Помошта од други лица за нега, поддршка и помош при основните дневни потреби се перцепират како витален, но исто така и како постојан предизвик, особено за пациентите со поголеми функционални оштетувања. Пациентите ги потврдуваат овие недостатоци кои се претежно практични, особени при ангажирање на надворешни негуватели. Во овој контекст, континуитетот на грижа од страна на доверливи негуватели е перцепирано како доста важно во одржување на приватноста, достоинството и удобноста. Големите празнини во формалната грижа се исполнети со неформална грижа од страна на семејството и пријателите. Практично, грижата и поддршката од страна на семејството и пријателите е препознаена како неодржлива со текот на времето. За некои од родителите прифаќањето на овој чекор претставува траума, поради желбата за заштита на нивното дете со спинална мускулна атрофија [15].

Психолошката благосостојба и нејзиното влијание

Вознемиреност како одговор на промените во физичката функција

Пациентите опишуваат чувства на длабока тага како одговор на губењето на независноста која се јавува како резултат на падот на моторната функција. Некои од пациентите пак ја негираат оваа вознемиреност, на тој начин заштитувајќи се од губењето на моторната функција. Треба да се истакне важноста од препознавањето на светлината и сенката од емоционалните искуства на пациентите кои патем сакаат да бидат вреднувани, а не сожалувани. Сожалувањата понатаму може да доведат до фрустрации [15].

Стигма и социјални очекувања

Стигматизацијата влијае врз животот на пациентите. Кај дел од пациентите стереотипите од околината им претставуваат најголема пречка во остварување на своите визии. Стереотипите од различна природа се причина за да се запрашаат пациентите дали нивниот живот вреди да се живее [15].

Нега и поддршка од семејството и пријателите во адаптацијата и надминување на изолирање од заедницата

Силните мрежи составени од семејството и пријателите ја поддржуваат психолошката адаптација на овие пациенти. Поддршката од околината помага во процесот на самоприфаќање. Интересен е фактот и дека поддршката од останатите возрасни индивидуи со СМА доведува до чувство на удобност и инспирација. Практичните совети кои ги добиваат од постарите пациенти се непроценливи. Битно е да се напомене и дека голем број од пациентите осетиле на своја кожа изолација од околината поради физичките ограничувања. Поради ваквите искуства, се раѓаат осаменоста и копнежот за социјална вклученост. Радува фактот што пациентите споделуваат силна мрежа на контакти со социјалната околина [15].

Пациентите со СМА кои се на фармаколошки третман ги пријавиле следниве незадоволени потреби [16, 17]:

Симптомите на СМА сè уште се присутни [16, 17]

Третираните лица сè уште се подложни на прогресија на болеста [16, 17]

Интратекалната администрација не е секогаш можна поради сколиозата или ‹рбетната фузија [16, 17]

Некои пациенти не реагираат добро на лекот (ниска ефикасност) или искусуваат несакани реакции од лекот [16, 17]

Некои пациенти имаат тешкотии со пристапот до лекови [16, 17]

Предизвици во тек на дијагностицирањето, третманот и следењето

Доцнење на дијагноза и упатување

Многу лекари не ги препознаваат симптомите на СМА. Вкупната јавна свест за СМА е ниска. Потребни се повеќе посети на лекар, особено за „полесните“ форми. Доцнењето на дијагнозата е од недели до месеци. Особено, пациентите со тип 3 на СМА се дијагностицираат доцна во текот на тинејџерските години. [16, 17]

Недостиг на разбирање на важноста од мултидисциплинарната стандардна грижа

Здруженијата на пациенти играат клучна улога во поддршката на новодијагностицираните пациенти и нивните семејства. Стандардите за грижа варираат од земја до земја. [16, 17]

Исклучување на пациентот од системот на дијагностицирање и здравствена заштита

Емоционалната вознемиреност да се справи со дијагнозата е најтешкиот чекор за пациентот. Треба да се споменат и трошоците кои се директно поврзани со болеста. Родителите стануваат 24/7 старатели кои го реорганизираат својот живот. [16, 17]

Заклучоци

СМА е ретка, прогресивна, невродегенеративна болест која води до губиток на моторната функција и намален очекуван животен век [2, 4]. СМА е предизвикана од мутација и/или делеција на SMN1 генот [3]. Искуствата на пациентите со спинална мусклулна атрофија ја потенцираат потребата од развој и тестирање на добро структурирани, координирани програми за премин од детска во адултна медицинска грижа, прилагодени да ги задоволат потребите на пациентите со СМА. Идните истражувања потребно е да обезбедат проценки за распространетоста, товарот и трошоците поврзани со психолошкката вознемиреност кај оваа популација, како и за развој на ефективни и одржливи услуги за психолошка нега, нови интервенции и ресурси. И покрај напредокот во разбирањето и откривањето на лекови за СМА, се уште постојат незадоволени медицински потреби.

Conflict of Interest: None declared

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SPONTANEOUS PASSAGE OF A GIANT URETERAL STONE IN A 58 YEAR OLD WOMEN

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ABSTRACT

Giant ureteral calculi are defined as stones greater than 5 cm in length or circumference. These giant calculi can cause blockage of the ureter, dilation of the kidney and also decreased kidney function if not treated in time. The aim of this case report is to present maybe the first report of spontaneous passage with a spontaneous elimination of a giant stone from the distal ureter toward urin bladder and afterward out from the urethra. We present a case of a 58 year old woman with a giant stone on the distal part of the left ureter with consequent ureterohydronephrosis. She was a low stature, obese, with hypertension and diabetes mellitus type 2. Patient was proposed and planned for open left ureterolithotomy which she refused with the excuse that she is obese and with diabetes. Her next visit to our unit was after 3 months where in our surprise, with a cloth on her hand she held a giant stone 5,2 cm in length 1,2 cm in width and 32 grams in weight. The stone was with a very soft surface without any thorns. To our knowledge in the literature there is no data of spontaneous passage and spontaneous elimination of a such giant stone, and this it might be the only case reported, to date.

Key words: giant ureteral stone, spontaneous passage, spontaneous elimination, ureterolythotomy

INTRODUCTION

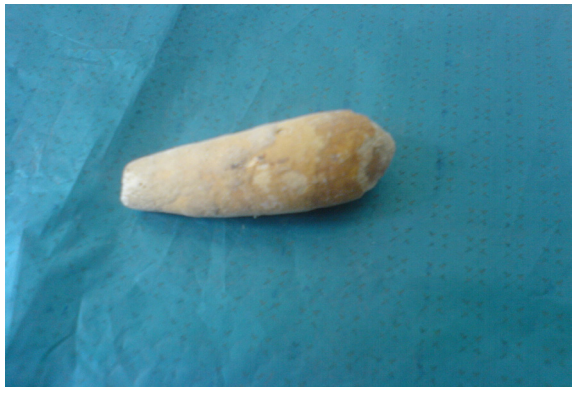
The stones are composed of calcium oxalate or phosphate in 80% of cases. Struvite (magnesium ammonium phosphate), cysteine and uric acid are other types of stones. The spontaneous passage of the ureteral stones is depends upon both the location (proximal, mid, and distal ureter) and size of the stone. Blockage of ureter due to stones can lead to ureteric colic. Ureteric obstruction can leading to impaired renal function and dilation of kidneys [1]. A number of factors must be considered in determining the optimal treatment for patients with renal or ureteral calculi. These factors may be grouped into four broad categories: stone factors (location, size, composition, presence and duration of obstruction); clinical factors (symptom severity, patient's expectations, associated infection, obesity, coagulopathy, hypertension and solitary kidney); anatomic factors (horseshoe kidney, ureteropelvic junction obstruction and renal ectopia); and technical factors (available equipment, expertise and cost). The guideline for the management of ureteral stones include: conservative management, medical expulsive therapy, active intervention with either shockwave lithotripsy (SWL) or ureteroscopy (URS), factors affecting SWL treatment success, optimizing success, and special considerations (e.g., pregnancy, urinary diversion) [2]. The global incidence of urinary stone disease is estimated to be 2–20%, whilst the lifetime prevalence of urolithiasis is reported to be 5–12%. The choice between watchful waiting and active management until spontaneous passage is the main problem for the urologist when managing patients with ureteric stones [3]. Factors such as calculus location and size, the degree of hydronephrosis and pain, and perinephric stranding have been shown to provide general predictions of the probability and duration of passage. These characteristics allow the urologist to provide the patient with a general prediction of the outcomes [4]. A ureteral stone is a kidney stone that passes down into the ureter. The likelihood of spontaneous passage of ureteral stone is related to both stone size and location. Therefore most of the small ureteral stones pass spontaneously. However, stones larger than 1cm in diameter and weighing more

than 0.1 gram are less likely to be passed. Larger stones are lodged usually in the lower narrower part of the ureter. After the stone has resided in the ureter for some time, the longitudinal diameter becomes greater than the transverse diameter resulting in an elongated shape 2. In general, ureteral calculus is single and less than 2 cm in length. Occasionally, ureteral stones are multiple and can be as large as 5 cm in size. Ureteral weighing more than 50 gm in weight and about 10 cm in length is called as giant calculus [5]. The prevalence of urolithiasis, or urinary stone disease (USD), is increasing among adults and children worldwide. Because the most common symptoms of USD include severe flank and abdominal pain, nausea, vomiting and hematuria, patients often present to the emergency department for treatment [6]. Approximately 13% of men and 7% of women will be diagnosed with a kidney stone in their lifetime, and the numbers seem to be increasing. Urinary stone disease is a common disorder accounting for 122 of 100,000 outpatient visits and affecting 0.2% of the population annually.1,2 With recurrence rates for urolithiasis as high as 70% over 10 years, nephrolithiasis leads to significant morbidity and lost productivity [7]. Stone recurrence depends on geographic, climatic, ethnic, dietary, and genetic factors. Prevalence varies from 1% to 20%. Stone composition is the basis for further diagnostic andmanagement decisions. Stones can be classified by cause, aetiology of formation, composition, and risk of recurrence. Further classifications are based on stone size and location or X-ray characteristics (plain X-ray appearance on kidney-ureter-bladder [KUB] radiography). Non–contrast-enhanced CT (NCCT) can be used to classify stones according to density and composition [8]. In a patient who has a newly diagnosed ureteral stone <10 mm and whose symptoms are controlled, observation with periodic evaluation is an option for initial treatment. Such patients may be offered an appropriate medical therapy to facilitate stone passage during the observation period [9]. Besides routine history and clinical examination, investigations of patients with suspected ureteric colic include plain abdominal radiography, ultrasound, intravenous urography and computed tomography [10].

CASE REPORT

We present a case of a 58 year old woman, when she came to our urology unit in May 2016 complaining on left flank pain and dysuria for more than 5 months. Urinalysis revealed microscopic hematuria and pyuria. The history of her illness indicated that the patient continuously used analgesics to reduce her pain. Urine culture was positive for Proteus mirabilis and was treated with ceftriaxone 1 g twice a day for 5 days. Serum creatinine level was 130 mmol/, urea 12,4 mmo/l, Hemoglobin 14.6 g/dL and other laboratory studies revealed no significant abnormalities. She was with high blood pressure 160/95 mmHg and with diabetes mellitus type 2 where glycemia was 7,6 mmo/l. She was a low stature 157 cm in hight and obese with 89 Kg. Physical examination did not yield anything apart from tenderness in left costovertebral angle location. Ultrasound (US) detected hydronephrosis and hydroureter on the left side. A plain abdominal film (KUB) and computed tomography (CT) showed a giant stone on a left distal ureter measuring up to 5 cm in length causing ureteral obstruction. Patient was proposed and planned for open left ureterolithotomy in view of the large size of calculus and due to impaction of stone in the vesico-ureteric junction. But, she refused the operation with the excuse that she is obese and with diabetes. We warned her that if not operated she would lose her kidney and may cause other complications. She chuckled and while laughing said, if “I lost one kidney, I got the other”. This was her final decision. Her next visit to our unit was after 3 months where in our surprise, with a cloth on her hand she held a giant stone 5,2 cm in length 1,2 cm in width and 32 grams in weight. It’s quite unbelievable and impossible that such a large stone can pass through the ureter spontaneously toward urine bladder and what’s even

more shocking is to exit it out of the urethra. The stone was with a very soft surface without any thorns (Figure 1).



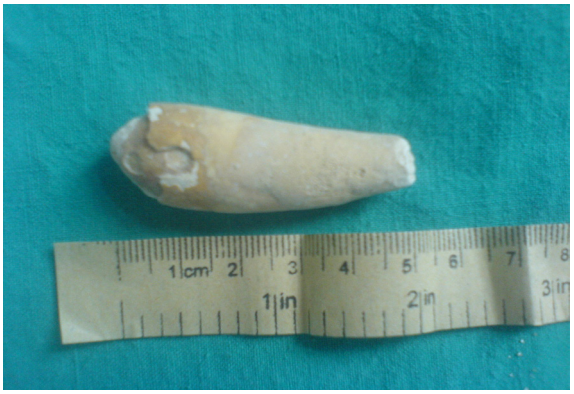


Figure 1: giant stone with soft surface and no thorns 5,2 x 1,2 cm and 32 gr weight

The new laboratory studies revealed no significant abnormalities (urea and creatinine in serum were normal) and ultrasound detected no signs of hydronephrosis. To our knowledge there are no cases reported in the literature, and this might be the only case reported, to date. In the literature there is no data of spontaneous passage and spontaneous elimination of a such giant stone.

DISCUSSION

To the best of our knowledge, there are no published case reports of ureteral calculi measuring 5 cm or more. Giant ureteric stones are rare. However the etiology and pathology of these stones remain unclear. The longest stone was reported by Taylor in 1934 which was 21.5 cm in length [11], Mayers indicated the largest ureteral stone (11 × 5.5 × 5 cm), which weighed 286 g [12], and Sabnis also reported a giant stone with 13 cm of length and 90 g of weight [13]. Most of these giant stones were distal ureteral calculi. This may be due to their role in distal ureteral obstruction, which is a factor that increases the diameter of the stone [14]. There are various techniques in the management of ureteral stones, including extracorporeal shock wave lithotripsy (ESWL), open surgery, medical expulsive therapy (MET), ureteroscopy (URS), laparoscopy (LAP), and PCNL. Drainage with an internal ureteral stent is also common due to its positive effects on morbidity. Nowadays, ESWL and PCNL are the two most commonly performed treatments since they are minimally invasive surgical methods that significantly decrease the morbidity of stone removal. In these techniques, success is determined by fragmentation rates and the size of the remaining stone fragments [15]. Large ureteral stones frequently cause pain and infection because of stone impaction and pelvicaliceal system obstruction. This condition may result in partial or even complete loss of the renal functions if the treatment is not done promptly. Currently ESWL and URS are the most widely used noninvasive treatment modalities for ureteral stones [16]. Various treatment methods are available for ureteric stones, varying from active surveillance or minimally invasive management to open or laparoscopic intervention. Avoiding operative stress, or merely compliance with medication, are of concern to both the physician and patient. However, the problem is how and when to make the decision. Delaying this decision can be associated with an increased risk of complications. Therefore, predicting the possibility of spontaneous stone passage is the key to deciding to opt for active surveillance of a ureteric stone. Many factors could influence the spontaneous passage of a ureteric stone in the course of expectant treatment. However, the absence of perinephric fat stranding (PFS) and tissue-rim sign (TRS) are significant predictors for stone passage. These signs, that can be easily identified at the initial evaluation of the patient, should be considered when deciding to use expectant management. [3]. There is total agreement that stone size is the most important factor for predicting the spontaneous passage of calculi. For urologists managing patients with ureteric stones the uncertainties about how long (if at all) it will take for a stone to pass spontaneously is a common concern. However, this does not seem to be discriminative enough when calculi are of mid-size. At this stage the urologist needs more information to make a valid clinical decision, but there is no clear result as to which factor should be considered first and what are the important interactions between all the factors [4]. A ureteric stone recently expelled from the kidney is usually round or ovoid and as it descends, it becomes date shaped. Stone that lodges in the ureter, may cause acute or dull pain, obstruction and sometimes fever. Sometimes it may even remain asymptomatic. Usually severe colicky pain prompts the person to seek medical help. Prolonged obstruction leads to atrophy of renal parenchyma and functionless and destroyed renal unit above the ureteric calculus. Although giant ureteral stone may form in patients with normal ureteral anatomy, many authors have reported that giant ureteral calculi form in patients with congenital ureteral anomalies [5]. Watchful waiting and medical expulsion therapy are the 2 most commonly used conservative methods that have been increasingly more frequently used in the treatment of distal ureteral stones to allow spontaneous stone passage, especially in patients who have less than grade 2 hydronephrosis [6].

We demonstrated that left-sided ureteral stones seem to pass significantly more often than right-sided in some analyses. The reason might be that the right ureter is typically adherent to the peritoneum, in contrast to the left ureter, providing a better peristalsis in the left ureter [17]. According to EAU/AUA, although patients with ureteral stones >10 mm could be observed or treated with medical expulsive therapy (MET), in most cases such stones will require surgical treatment. No recommendation can be made for spontaneous passage (with or without medical therapy) for patients with large stones [9]. This case report presents maybe the first report of spontaneous passage with a elimination of a giant stone from the distal ureter toward urin bladder and afterward out from the urethra.

CONCLUSION

Giant ureteral stones (more than 5 cm in length or 30 gram in weight) are extremely rare in the literature. Also, there is no report of spontaneous passage with a spontaneous elimination of a giant stone of 5 cm from the distal ureter toward urin bladder and afterward out from the urethra. Al data from the literature for the managament of a giant ureteral stones prescribes a different procedures of the treatment like minimally invasive treatments, laparascopic and open surgery.

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CYSTADENOFIBROMA LIGAMENTI UTERI LATI LATERIS SINISTRI; CYSTIS PARATUBARIS MESONEPHRICUS LATERIS SINISTRI; THEIR INCIDENCE, DIAGNOSTIC CHALLENGE AND TREATMENT

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ABSTRACT

Broad ligament cystadenofibroma and paraovarian mesonephric cysts and other paraovarian masses are part of the adnexal pathology found in all age groups of females from fetuses to adult women, more commonly from 3rd to 5th decade. They all contain 10-20% of all adnexal masses. Paratubal cysts, including Hydatid cysts of Morgagni, are of paramesonephric origin, while paraovarian ones originate from Wolffian ducts. Borderline or malignant tumours occur in 2-3% of cases. Broad ligament cystadenofibroma is a rare entity with only few articles published, and scarce data concerning their incidence. Paratubal mesonephric cyst is more common than broad ligament cystadenofibroma but there is also no data on their incidence.

This article presents a case of concomitant presence of paraovarian cyst and Broad ligament cystadenofibroma in a 19-year-old patient, with no history of pregnancies. The patient sought medical attention due to abdominal pain. Laboratory tests showed a reduction of haemoglobin and hematocrit values, tumour markers Ca 125 and CEA were within normal limits, bHCG was negative. Transvaginal ultrasound and color Doppler revealed cystic adnexal mass on the left side measuring 43 mm of dimension, and a small amount of fluid in Douglas pouch (Figure 1). Due to abdominal pain and reduction of haemoglobin values, laparotomy was indicated and extirpation in toto of the tumor was performed. The histopathology confirmed the benign nature i.e. paraovarian cyst and Broad ligament cystadenofibroma. The case is presented regarding to extremely rarity of Broad ligament cystadenofibroma, possible urgent conditions of paratubal mesonephric cyst, way of treatment and their diagnostic challenge.

Keywords: cystadenofibroma of the Broad ligament; paratubal mesonephric cyst; adnexal pathology, paraovarian cyst, ultrasound diagnostic, urgency, pelvic pain

INTRODUCTION

Anatomical localization of Broad ligament cystadenofibroma and paraovarian mesonephric cysts is between the ovary and the tubes in the small pelvis [1]. Paraovarian masses can be benign, but rarely in 2 to 3% of cases may have malignant nature. They occur in all age groups, from fetus to adult women with a greater prevalence between 3rd and 5th decade. The origin of paraovarian cysts is from the remnants of the paramesonephric Mullerian and the mesonephric Wolffovian ducts, from their caudal and cranial segments which remain in the mesovarium and form the epoophoron and the paroophoron, the structures from which paraovarian cysts can form in the future [2]. The genital tract of the woman originates from the paramesonephric Mullerian ducts [1]. Paraovarian cysts arise from the mesothelium of Mullerian and Wolffovian which are formed with an invagination of the embryonic

mesothelium. On the other hand, Broad ligament cystadenofibroma is extremely rare tumor which has mixed mesothelial and mesenchimal origin from the mesothelium and fibroblasts of the endopelvic fascia. The paraovarian cyst malignancy is rare and is represented by 2-3% of cases and can spread from borderline to malignant paraovarian cysts [3].

The symptomatology of Broad ligament cystadenofibroma and paratubal mesonephric cyst varies from a feeling of pressure, bloating, pain all of that depending mostly on their size. Asymptomatic cysts are usually up to 8 cm in size and they are detected accidentally during autopsy or diagnostic imaging of another disease. On the contrary, larger cysts that can reach up to 20 cm usually develop more dramatic clinical symptomatology as a result of pressure on the surrounding structures resulting in pain, especially if the rupture, cystic haemorrhage or torsion of the cyst was occurred.

The first diagnostic tool is ultrasonography which is limited in the differential diagnosis between the ovarian and paraovarian cysts. Computerized tomography and magnetic resonance imaging can be helpful in the reaching diagnosis. The risk of malignancy is greater in cysts whose dimensions exceed 5 cm [4].

The management of these adnexal masses depends on symptomatology. If their size is less than 6 cm can be managed by monitoring the patient, even in the postmenopausal age. According to the American College for Obstetrics and Gynecology guidelines, all adnexal masse which don't cause pain, bloating and do not show signs of malignancy on ultrasonography, such as septs, murals nodules, murals papillae, haemorrhagic components, and thickened walls, as well as CA-125 marker is below 35 UI, can be monitored without operative treatment. The frequency of controls depends on the initial finding, the presence of pain, bloating, size and ultrasonographic characteristics.

The therapeutic approach is by applying laparoscopy with meticulous intent not to cause rupture of the cyst which can cause spreading of its components resulting with peritoneal dissemination if it is with malignant nature. Urgent conditions may require laparotomy.

CASE REPORT

We describe a case of a 19-year-old girl which was admitted in our clinic with abdominal pain and cystic adnexal pathology. The personal history included menarche at 12 years, regular periods, no pregnancy before. She denied having experienced weight loss, fever, chills, night sweats, urinary tract symptoms or other gastrointestinal complaints. The clinical examination revealed a good physical appearance. There was a pain on the left down abdominal quadrant deep in abdominal palpation. On pelvic exam, a smooth, round, rubbery mass, non-adherent to the surrounding tissues and no vaginal bleeding was found. Laboratory tests showed reduced haemoglobin and hematocrit values, tumour markers CA 125 and CAE were within normal limits, bHCG was negative. Transvaginal ultrasound 2D and colour Doppler revealed a cystic adnexal mass with 43mm on the left adnexal region (Figure1). There was also a small amount of fluid in the Douglas pouch. A normal uterus and normal right ovarium were described.

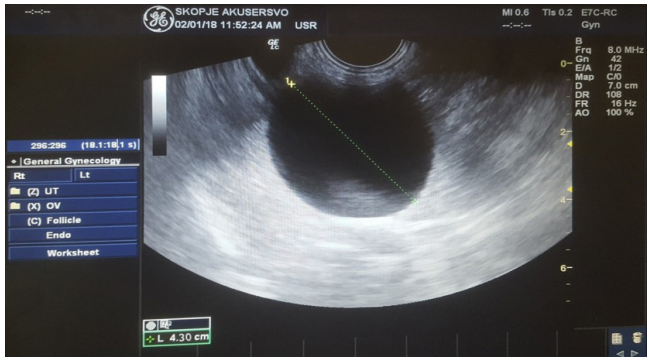


Figure 1. Pelvic ultrasound of the patient revealed unilocular cyst with translucent liquid.

Intensity of the pain increased during hospitalization, there was also reduction of the haemoglobin and hematocrit values. Laparotomy with transversal Pfannenstiel section was indicated, and extirpation in toto of the tumor was performed. Intraoperative there was cystic hyperemic formation on the left fallopian tube with dimensions of 50mm with signs of internal haemorrhage and torsion 3 times around its axis. The cyst had no attachments to the abdominal wall, intestine, or mesentery and it was successfully removed during the procedure. The uterus, both ovaries and right fallopian tubes were normal. Patient recovery was quick and uneventful.

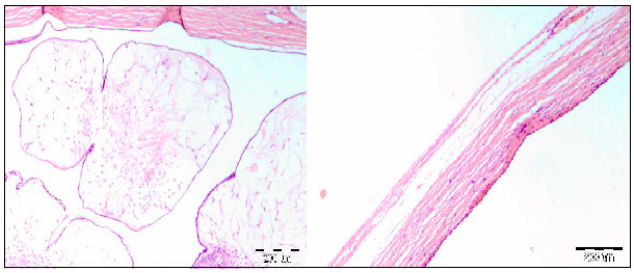
Histopathological examination of the Operative Material revealed both Cystadenoma of the Broad Ligament (Figure 2A) and Paratubal Mesothelial Cyst (Figure 2B), without signs of cytologic atypia.

Figure 2A. Photomicrograph of the Broad Ligament Cyst demonstrating broad, variably cellular stromal to

edematous pappilae, covered by a single layer of cuboidal to columnar epithelium. (Haematoxylin & Eosin, original magnification x 40).

Figure 2B. Photomicrograph of the Paratubal Cyst composed of thin wall of fibrous stroma lined with single layer of flat cells. Haematoxylin & Eosin, original magnification x 40).

Cytology of the peritoneal washing was classified as group I.



A B

Figure 2. A. Broad ligament adenofibroma; B. Paratubarian mesonephric cyst

DISCUSSIONS

Broad ligament cystadenofibroma is extremely rare pathology i.e. there is only one reported case of paraovarian cystadenofibroma from February 2016 [9] in which is quoted that previously there was only one reported case of paraovarian cystadenofibroma [10]. In spite of the fact that paratubal mesonephric are more common, there is no data on their incidence. Both tumours are documented as paraovarian masses, which in most of the cases are of benign pathology, especially when they are less than 5 cm in diameter and when ultrasonography cannot detect pathognomic ultrasound signs of malignancy, such as: septs, intracystic nodules, papillary growths, solid or hemorrhagic intracystic masses and thickened walls. The malignancy of paraovarian cysts is less frequent in 2-3% of cases, more commonly in larger cysts above 5 cm, which have the aforementioned pathognomic ultrasound signs [4]. Tumour markers can also be used when malignancy is suspected.

Appropriate diagnosis is challenging especially when paraovarian, paratubal cysts from true ovarian cysts need to be differentiated. The first diagnostic tool is ultrasonography, which can reveal cysts suspected of malignancy [5,6]. The challenge is especially in the larger cysts. There are no pathognomic ultrasound signs that would help differentiate paraovarian from the ovarian cysts [7], but a clear hyperechogenic border between the ovarian tissue and the cyst can be helpful. Paraovarian cysts may be mobile in relation to the ovary, however, it depends on the size of the cyst, their location in the small pelvis and the relationship with the uterus and the ovary. In differential diagnosis, we encounter simplex cysts, cystadenofibromas, hydrosalpinx, functional cysts, serous cysts, peritoneal inclusion cyst, mucocele of the appendix, uterine leiomyoma, adenomyosis, spinal meningeal cyst, unicornuate uterus, lymphocele, cystic degeneration of lymph nodes, lymphangioleiomyomatosis, hematoma, and abscess. All these entities can be poorly interpreted on ultrasound such as ovarian cysts [5]. Other diagnostic tools include computed tomography and magnetic resonance imaging.

Complications of broad ligament cystadenofibroma, parartubal mesonephric cyst and other paraovarian cyst are torsion, rupture and haemorrhage which can lead to intraperitoneal bleeding and other complications like infection, pelveoperitonitis and peritonitis. Torsion causes lower abdominal pain which can mimic appendicitis. Laparoscopic surgery is an option in the management of adnexal masses; however, rupture or puncture of masses should be avoided in favor to prevent to prevent potential tumour dissemination in the event of a malignancy. Excision of cyst is needed with preservation of adnexa especially the ovary. Preservation of the adnexa in female adolescents is critical, and minimally invasive approaches should be used where is possible. Laparoscopic cystectomy is possible in smaller cysts with a benign ultrasonographic finding. On the contrary, in larger cysts which cause pain, haemorrhage, effusion as a result of rupture and torsion, laparotomy should be performed.

CONCLUSION

Broad ligament cystadenofibroma is extremely rare combined stromal-epithelial tumor. Only two other cases of paraovaian serous cystadenofibromas has been reported [9,10]. We want to highpoint that its imaging is often complicated because its cystic- to solid-appearance often resembles as a malignant tumor. Preoperative differential diagnosis to exclude malignancy or borderline malignancy is difficult with cystadenofibromas, particularly in a young woman, when the preserve of fertility need to be priority. Therefore, the ongoing data collection with combined diagnostic imaging and

histopathology is most important.

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9. A case of paraovarian serous cystadenofibroma that showed a malignant potential in image inspection Rie Miura, Atsushi Fukui, Ayano Funamizu, Tatsuhiko Shigeto,Yoshihito Yokoyama, Hideki Mizunuma Department of Obstetrics and Gynecology, Hirosaki University Graduate School of Medicine, Hirosaki, Aomori, Japan
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MALE SYSTEMIC LUPUS ERYTHEMATOSUS, AND CHALLENGE IN MALE LUPUS NEPHRITIS TREATMENT

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ABSTRACT

BACKGROUND: Systemic lupus erythematosus (SLE) is an autoimmune disease. In this disease, the immune system of the body mistakenly attacks healthy tissue. It can affect the skin, joints, kidneys, brain, and other organs.

The cause of SLE is not clearly known. It may be linked to the following factors: Certain medicines

Case presentation: We present 44 years old male with SLE- Lupus Nephritis. His disease started with swelling in the elbows, shoulders, hands, knees, alopecia and other symptoms. We got challenge for treatment of this patient and we use treatment with werry toxic medicamentations. He was diagnosed with SLE before he consult at our clinic of Nephrology. He consult as the time he got Lupus Nephrit (proteinuria and undr-knee oedemas). We make renal biopsy couse there are 6 classes of lupus nephritis, so we cen and treat him by protocol for the class of Lupus Nephritis he has disease. We got successful to control the LN.

The second case involved a patient who was first diagnosed with SLE at the age of 14 and began treatment at the Pediatric Clinic. After a few relapses in the following years, he receives Cl. for Nephrology appropriate and by age, for treatment with methylprednisolone therapy by protocol.

Keywords: Systemic lupus erythematosus, Genetic, Environmental, Hormonal, Lupus Nephritis, biopsy.

INTRODUCTION

Systemic lupus erythematosus (SLE), is an autoimmune disease in which the body's immune system attacks healthy tissue in many parts of the body, by mistake. SLE is also known simply as lupus. There are several explanations for the term lupus erythematosus. Lupus is Latin for "wolf", and "erythro" is derived from ερυθρός, Greek for "red." [1,7]

Symptoms vary between people. Common symptoms include swollen and painful joints, mouth ulcer, fever, feeling tired, swollen lymph nodes, chest pain, a red rash which is most commonly on the face. Often there are periods of illness, called flares, and periods of remission during which there are few symptoms. [12]

The cause of SLE is not clear. It culd involve genetics, of environmental factors, or the same factors together. Sunlight, smoking, female sex hormons, infections, and other factors can incrase the risk. [4]

When we speak abouth identical tweens, when one is affected there is 24% chance the other one will be as well.

We write about male SLE, because between 80 and 90 percent of those with the SLE disease are women, who typically develop the disease between the ages of 15 and 44. Lupus, like many autoimmune diseases, affects females more frequently than males, at a rate of about 9 to 1. .[6 The X chromosome carries immunological related genes, which can mutate and contribute to the onset of Lupus. The Y chromosome has no identified mutations associated with autoimmune disease.

There is no clear consensus on why, but many experts point to environmental factors over genetics ones.

A male get only 10 percents of the disease, usually SLE manifest clinically before the age of 50 years old male. When while women are affected more often, lupus in

men tends to be more severe and have greater organ involvement. The difference in frequency between the sexes is often attributed to hormone imbalances. What we can see often is female lupus patients with really high levels of estrogen, and male lower levels of testosterone and more estrogen than normal.

The early symptoms of male lupus are very non-specific in terms of aches and pains, mouth ulcers and rashes which are often difficult to diagnose. Reports often suggest men with lupus have a higher frequency of involvement of the pleura and pericard of the lung and heart- called Serositis.. Also pneumonitis, pulmonary hypertension.

Men are more likely to develop nerve damage nerve damage- peripheral neuropathy, differences between men and women in terms of the number and type of antibodies and blood test abnormalities, haemolytic anemia, alopecia, seizures, vascular diseases, blood clots, discoid lupus, increased risk of epilepsy and kidney involvement.

When we speak about kidney involvement we cen say something about Lupus nephritis. Lupus nephritis is an inflammation of the kidneys caused by SLE. [11] [12] [16][17] It is a type of glomerulonephritis in which the glomerulus become inflamed. As the result of SLE, the cause of glomerulonephritis is said to be secondary and has a different pattern and outcome from conditions with a primary cause originating in the kidney.

Classification of Lupus nephritis:

Class I disease minimal mesangial glomerulonephritis
Class II disease mesangial proliferative glomerulonephritis
Class III disease focal glomerulonephritis
Class IV disease diffuse proliferative glomerulonephritis
Class V disease membranous glomerulonephritis
Class VI, or advanced sclerosing lupus nephritis

Tabe 1- classification of Lupus nephritis.

Signs and symptoms include fever, edema, high blood pressure, joint pain.

The diagnosis of lupus nephritis depends on blood tests, urinalysis, X-rays, ultrasound scans of the kidneys, and a kidney biopsy. On urinalysis, a nephritic picture is found and red blood cell casts, red blood cells and proteinuria is found. The World Health Organization has divided lupus nephritis into six stages based on the biopsy. [9] [13]

The principal goal of therapy in lupus nephritis is to normalize renal function or, at least, to prevent the progressive loss of renal function. Therapy differs depending on the pathologic lesion. It is important to treat extrarenal manifestations and other variables that may affect the kidneys.

Corticosteroid therapy should be instituted if the patient has clinically significant renal disease. Use immunosuppressive agents, particularly cyclophosphamide, azathioprine, or mycophenolate mofetil, if the patient has aggressive proliferative renal lesions, as they improve the renal outcome. .[5] [10] [14] [15]

CASE REPORT

1-case

A 44-year-old man diagnosed with Systemic lupus erythematosus. Initially, the disease began with swelling of the elbows, shoulders, arms, knees, hypertensive arterial disease, anemia, metacarpo-phalangeal and proximal inter-phalangeal joint pain associated with lumbar pain, morning stiffness.

The patient is consulted by a rheumatologist and hospitalized at the Rheumatology Clinic.

After blood tests and immunological tests (antinuclear antibody (ANA) testing and anti-extractable nuclear antigen (anti-ENA), anti dsDNA), which are the basic test of serological testing for SLE, treatment with SLE was initiated and diagnosed. with corticosteroids and anti-malarial drugs.

After a while, the patient also began to manifest knee edema, swollen knee and ankle edema, anemia, high blood pressure and consulted at our Neurology Clinic. Laboratory analyzes showed Hg-78g / L, HCT-0.31, WBC-4.6, Glikemia-6.0, Urea-12.5, Creatinine-136, Total Protein-48, Alb-19, Ca- 1, 8, Proteinuria / 24> 5.43g / L (9.7 g / diuresis) and thrombocytopenia in favor of Lupus Nephritis

During our hospitalization at our Nephrology Clinic, we did a kidney biopsy to diagnose which class of Lupus Nephritis is at baseline. The result showed Lupus Nephritis class IV, V and VI, glomerulonephritis endocapsularis and extracapsularis. We started protocol treatment with methyl-prednisolone shock, then continued corticosteroid therapy with peer. Os , diuretics, and ambulatory treatment with cyclophosphamide per protocol (Endoxan).

Renal biopsy show:

Glomerulonepritis endocapillaris et, extracapillaris partem membranosa (lupus nephritis class IV, V, VI).

Microscopically, the slices show 13 glomeruli with surrounding corticomodulatory tuberculosis. the glomeruli are of impaired structure. Bowman's membrane is fibrous thickened, coated with activated parietal epithelium that is adhered to visceral epithelium. parietal epithelium proliferated in 3 of the glomeruli. glomerular rearrangements are increased, with increased cellularity and lobular activity, leukocyte infiltration and decay, with thick basal membranes and present double nom track changes. Tubulo-interstitial nephritis shows changes in the severity of active chronic tubular-interstitial-nephritis with tubular atrophy, and blood vessels with pronounced onion skin lesions.

The biopsy results showed Lupus Nephritis class IV, V and VI, glomerulonephritis endocapsularis and extracapsularis. Classical class III and IV is one of the most destructive classes, we started with corticosteroid treatment pulse methylprednisolon 500mg daily x 3 doses, iv cyclophosphamide 1 g given monthly over a period of 6 months, and antihypertensive drugs –Tabl Nifedipine 20mg 1x1 a day. The treatment was conducted according to the KDIGO protocol.

Some hospitalizations were also treated with blood derivatives and plasma because of low blood count parameters. We have achieved success in the treatment of controlling SLE. At the next checkup the patient is stabilized with a lab. analyzes: Hg-157g / L, Er-5.6 (10x12 / L), Tr-225 (10x12 / L), Alb-37g / L, incl. pro-63g / L, Urea (serum) -6.6, Kr (serum) -87, 24-proteinuria 4.8 and 1.6 liter.

Tabe 2- Tpeatment protocol for initial therapy in class III/ class IV LN:

Medication	Dosing
INDUCTION	THERAPY
MMF (mycophenolate mofetil)	2-3g IV/po daily x 6mon.
Cyclophosphamide	Euro Lupus -500mg IV every 2 wk x 6 doses High dose: 500-1000mg/m2 IV montly x 6 doses
Methylprednisolone	Pulse:500-1000mg IV daily x 3 doses, followed by 0,5-1mg/ kg/day of oral glucocorticoid tapered to minimal effective dose
MAINTENANCE	THERAPY
MMF (mycophenolate mofetil)	1-2g po daily x 3y
Azatioprine	2mg/kg po daily x3y
ADJUNCTIVE	TREATMENT
Hydroxychloroquine	200-400mg po daily

Tabe 3- blood and urine parameter for hospitalization in our clinic of Nephrology and period when we use treatment with endoxan.

				1. endoxan	2. endoxan		3. endoxan	4. endoxan	5. endoxan	6 endoxan
Date	Ref. val.	24/4/17		08/5/17	13/06/17	13/6/17	11/07/17	11/08/17	1/9/17	2/10/17
Er	5,5	3,78		3,68	3,8		3,87	3,9	4,58	5,51
Tr					211		237	186	171	192
Le	4-9	4,6		12,3	10,9		6,5		9,3	8,4
AF	11-85						55		67	64
A ST	4-34				19		18		21	26
ALT	3-45				21		15		14	22
Glik	6,5	6		6	5		6,38	5	4,58	5,21
Urea	3-7,8	12	90	15,8	15		13	13	72	9,1
Creat	109	136	131	107	127		127	124	94	109
Ac Ur	450				522		610	413	447	504
t. prot	65-80		48	42	51	62	57	62	63	66
Alb	35-50		19	19	23	23	31	23	37	34

Na	135-145			141	137		140	140	139	138
K	3,8-5,5			4,2	4,6		4,1		4,4	3,9
Ca	2,1-2,6		1,8	1,82	2,1		2,03	2,04	2,16	2,16
Diure.-L	-1,5	9000	1600	1800						
Prot Kvant. g/L	0,1	5,43		3,1						
24/ Prot	0,2	9,75		6,01		2,83			2,0	1,8

2-Case

This is a patient who was first treated at a pediatric clinic at age 14 when SLE was diagnosed. Since then she has been treated 3 times at the pediatric clinic for relapses of primary disease. Over the past period, physicians' advice and therapeutic treatment have been regularly and regularly followed. The first relapse associated with skin rash, weakening, fatigue and lack of appetite associates it with a operated nail on the toe.

Last hospitalization, worsening nephritis, febrility, erythema of the face, skin rash, mild fatigue, nausea. Previously the underlying disease was relatively well controlled by alternate administration of Prenisolone 30mg / 48h and Imuran 100mg / dd with TA which was well regulated by the tablet. Tezimet 1x1 / 2 per day. At the last hospital assessment, relapses with elevated SE, profound anemia, proteinuria 7.4 g / L and positive ANA were observed. Due to leukopenia, Immuran is abolished.

During the last hospitalization, the following therapy is prescribed: 3 pulses of methylprednisolone 1 mg daily after completion of treatment with methylprednisolone given continuous pre-dialysis therapy 60 mg / 24 hours. Antihypertensive therapy Tabl. Cordipine Retard 1x1 daily and Tabl Tenzimet 1 + 1/2 day. Due to impaired glycoregulation he was placed on a diabetic diet. Recent results Se-58, Hb-95, Er-2.8, Le-6.3, Urine-alb +++, Urea-16.8, Kreat-172, clearance-0.5ml / s. Total prot-46, glycemia-5.9, C3-0.56, C4-0.34, IgG-9.39, IgA-1.47, IgM-1.38.

DISCUSSION

Lupus erythematosus is a chronic inflammatory disease that affects multiple organs or systems. It has an unknown, multifactorial etiology, in which the interaction of genetic predisposition and various hormonal, environmental and infectious factors appear to lead to a loss of immunological tolerance.

In humans, exacerbations of SLE during pregnancy, post partum and menstrual periods due to rapid hormonal changes are well documented, as there are numerous reports associating the use of estrogen-containing oral contraceptives and disease exacerbations. Men with lupus are fertile, sexually active and have normal reproductive history.

Because of the predominance of women in most studies, little is known about the disease in men. Studies suggest that the older men have higher mortality in one year than women with SLE, suggesting that even men with lupus have a more complex clinical course than women.

It has become increasingly clear that men with SLE have more seizures, immune-mediated anemia (low hemoglobin level) and lupus anticoagulant level that may lead to thrombogenesis.

CONCLUSION

In summary therefore, males certainly do develop Systemic Lupus Eritematosus but at far lower rates then women and this often contributes to the delay in diagnosing men with lupus.

There is no consensus on the presence of differences in the clinical manifestations between men and women with systemic lupus erythematosus. Further studies are warranted and more awareness should be given once sex differences affect the drug activity and it has been suggested that specific therapies should be developed based on gender.

We can say that treatment in Lupus Nephritis has been a real challenge, because include toxic medications. Patients with SLE and Lupus nephrit should always cooperate with doctors and apply their advice. They need to change many lifestyle habits and be verry patience. However it is a disease which is not curable and must be monitored continuously, due to the possibility of

exacerbation.

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A RARE CASE OF ERYTHROMELALGIA – CASE PRESENTATION

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ABSTRACT

Erythromelalgia is a rare condition that primarily affects the feet and, less commonly, the hands (extremities). It is characterized by intense, burning pain of affected extremities, severe redness (erythema), and increased skin temperature that may be episodic or almost continuous in nature. Studies suggest that erythromelalgia, is an disorder of some precapillary sphincters (constricted) causing deficient nutritive perfusion reflecting the local tissue resulting worsening the redness, warmth, and pain. Female patient, 8 years old. She was admitted with nodular changes on both legs (dorsal part of feet and left knee). Changes started 8 years ago but more sever last two years. She complained of painful changes and high local temperature (she didn't wear any socks). Generally she had atopic skin. Five years ago she was diagnosed with epilepsy (but she didn't use therapy anymore).

Key words: pain, erythema

What Is Erythromelalgia!

Erythromelalgia is a rare condition that primarily affects the feet and, less commonly, the hands (extremities). It is characterized by intense, burning pain of affected extremities, severe redness (erythema), and increased skin temperature that may be episodic or almost continuous in nature.

Studies suggest that erythromelalgia, is an disorder of some precapillary sphincters (constricted) causing deficient nutritive perfusion reflecting the local tissue resulting worsening the redness, warmth, and pain.

Because of the severity of the pain in erythromelalgia, and the lack of good pain medication then, there have been reports dating back to 1903 of amputation of the affected limb. In 1903 H. Batty Shaw reported that in three cases the pain was so severe, and that the affected extremities are so useless, that amputation was performed.[57]

Female patient, 8 years old, admitted with nodular changes on both legs (dorsal part of feet and left knee) changes started 4 years ago but more sever last two years complaint of painful changes high local temperature (she didn't wear any socks) generally she had atopic skin, Five years ago she was diagnosed with epilepsy (but she didn't use therapy anymore)

Fig.1 Symptoms of Erythromelagia

Routine blood analysis were in range except the leukocytosis

Urine normal

Eo= 8.9 (0.6 – 7.3)

IgE total= 1153 IU/ml (0-90)

Thyroid test normal

EEG normal

MR of the head normal

Staphylococcus aureus from eroded site

Skin biopsy (Univesitas Klinikum-Tubingen)

Patient was treated with: antibiotics (Erythromycin suspension a 250 mg every 6 hours 10 days) Aspirin tbl a 100 mg once daily, Ibuprofen/Paracetamol ,topical antibiotics Fucidin cream and corticosteroid Momethason cream emolients .

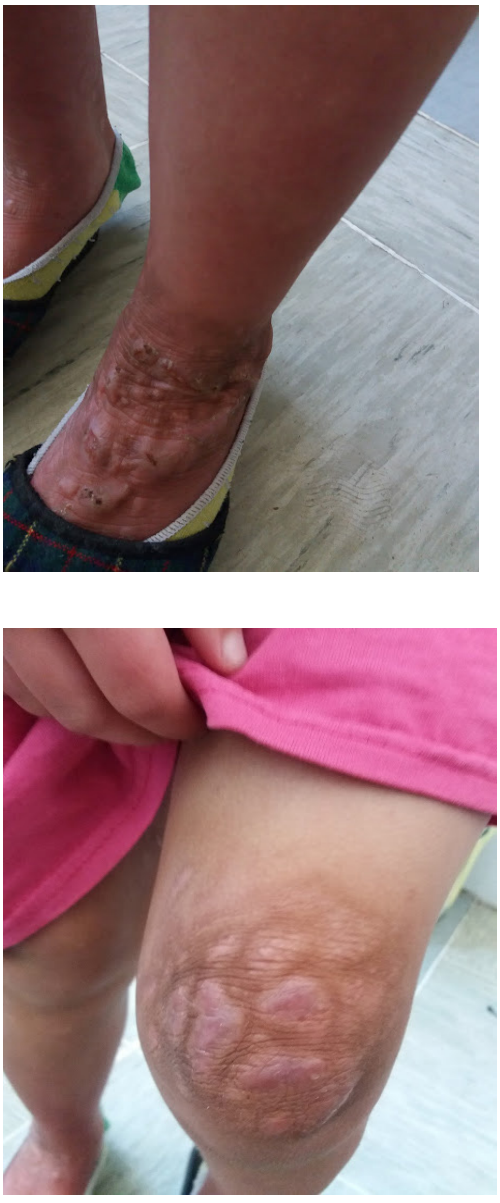
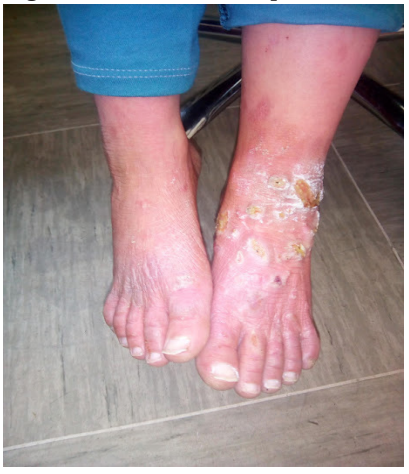
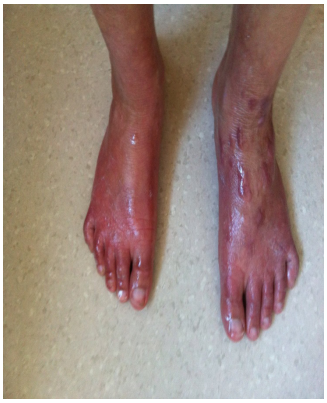


Fig.2 Pictures from the patient





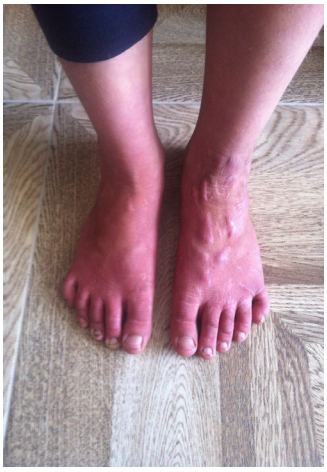


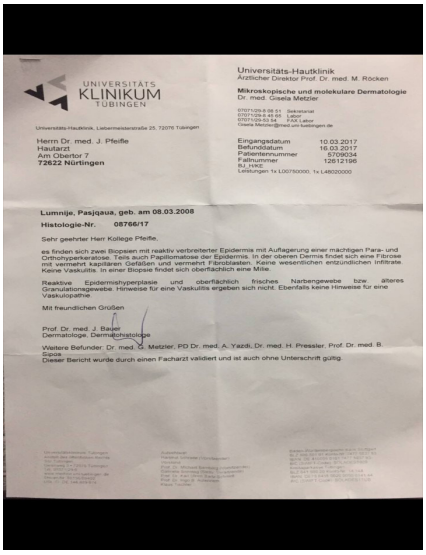
Fig.3 Photo before treatment and after treatment

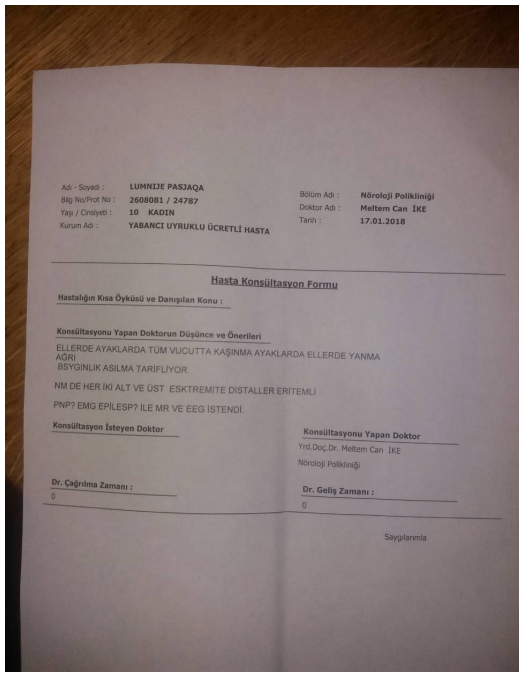
The histopathology describes

“epidermal acanthosis with a hyperplastic stratum corneum with para - and orthohyperkeratosis.

The upper dermis is fibrotic with an increased number of capillary blood vessels.

No vasculitis, no inflammation. No vasculopathy”





There are not a lot of studies that have investigated the prevalence of EM, so far only four have been conducted.[42] The mean of all the studies combined results in an EM estimation incidence of 4.7/100,000 with a mean of 1 : 3.7 of the male to female ratio, respectively.[42][43]

In 1997 there was a study conducted in Norway that estimated that the annual incidence of 2/100,000, with a 1 : 2.4 male to female ratio in this study population, respectively.[44] In 2009 there was a population-based study of EM in the USA (Olmsted County, Minnesota), that reported that the annual incidence was 1.3/100,000, with a 1 : 5.6 male to female ratio in this study population, respectively.[45] The incidence in this study of primary and secondary EM was 1.1 : 0.2 per 100 000 people per year, respectively.[45] A study of a single centre in the south of Sweden in 2012, showed the overall annual population-based incidence was 0.36/100,000.[46] In New Zealand (Dunedin) a study estimated that in 2013 the incidence of EM is 15/100,000, with a 1 : 3 male to female ratio in this study population, respectively.[43] This last study has an estimation that is at least ten times higher than the prevalence previously reported. This study recruited individuals based on self-identification of symptoms (after self-identification, patients where invited for an assessment of an EM diagnosis), instead of participants that are identified through secondary and tertiary referrals that was conducted by the other studies.[43]

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6. Erythromelalgia at eMedicine

Case report

REVERSE PIA FLAP IN HAND TRAUMA DEFECTS RECONSTRUCTION

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INTRODUCTION

Soft tissue reconstruction of the hand is always a complex problem to deal with because of the involvement of muscle, tendon and bone.There are different flaps at our disposal that can be used to cover these soft tissue defects.This flaps include local perforator based flaps, reverse flow forearm flaps, distant flaps like the groin and abdominal flaps and free flaps1. The reverse posterior interosseous artery (PIA) flap is based on reverse flow through the PIA via anastomosis with the anterior interosseous artery and the dorsal carpal arches near the wrist. The distal reach of the PIA flap is also limited to the MCPJ of the fingers and the IPJ of the thumb2.

ANATOMICAL DATA

The posterior interosseous flap is Type B fasciocutaneous flap based on the posterior interosseous artery, which lies invested by the fascial septum between the extensor carpi ulnaris and the extensor digiti minimi.

The artery gives off septocutaneous branches that spread out on the deep fascia to form longitudinal fascial arcades, as well as further branches that pass through the deep fascia to supply the underlying deep extensor muscles.

In the lower third of the posterior forearm, direct septoperiosteal branches to the ulna are also present3,4.

We found an anatomical study in 100 cadavers published in British Journal of Plastic Surgery (2001),54,28-33,by H.COSTA and other authors with very interesting results

The results confirmed that in 82 cases the artery originated from the common interosseous artery and in 18 cases it originated from the ulnar artery.

The posterior interosseous artery passed distally in the intermuscular septum and, in all of the 100 cadaveric dissections,was found to reach as far as the wrist, lateral to the ulnar head.

The anastomosis between the posterior and anterior interosseous arteries, underneath the extensor tendons, was present in all the dissections.

The artery gave off fasciocutaneous perforators along its length through the septum between the extensor carpi ulnaris and the extensor digiti minimi in all the cases. Three main distinct patterns of septocutaneous vessels were identified5.

MARKINGS AND SURGICAL TECHNIQUE

The surface marking of the posterior interosseous artery is drawn in a line between the lateral epicondyle and the ulnar head with the forearm in full pronation. A point 9 cm (range: 7.5-9.5 cm) distal to the lateral epicondyle marks the centre of the fasciocutaneous element of the flap.

The important anatomical consideration is that the fascial septum between the extensor carpi ulnaris and the extensor digiti minimi, in which the vessels lie, is orientated sagittally. In the distal half the artery is

relatively superficial but in the proximal half the septum lies underneath the extensor digiti minimi and so the vessel is more deeply situated.

This is the main reason why the dissection must be performed from distal to proximal.

The pivot point of the reversed vascular pedicle is about 1.0 cm proximal to the ulnar head and the pedicle length is about 7-8 cm 4,6,7.

Material and Method

5 distally based reverse flow posterior interosseous artery flaps were performed for hand reconstruction between 2010 and 2015.

Each patient received a full surgical explanation and a written consent was obtained.

All patients were males.

Their ages ranged from 35 to 57 years old.

The reconstructed areas included the dorsum of hand in 4 cases and the first web space in one case.

Two of the cases were post electrical burn sequelae, two others road accidents and one of them gun related injury.

We measured in all of them the pedicle and defect length

We decided to establish a one year period of follow-up for all the patients .

RESULTS

We had complete survival of the flap in four of the cases and only one partial survival

We had to deal with flap bulking in one of the cases after six months.

The patients satisfaction varied from 7 to 9 in a range scale from 5 to 10.

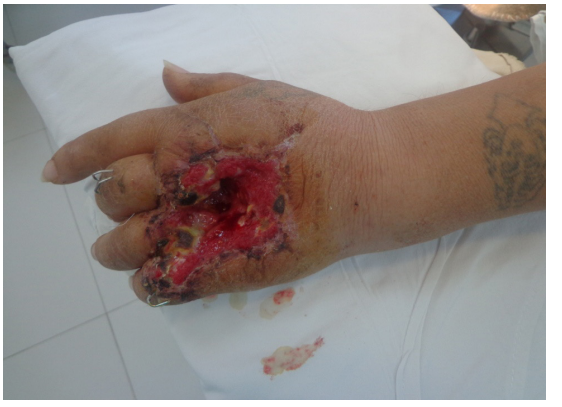
All donor sites were closed with STSG.

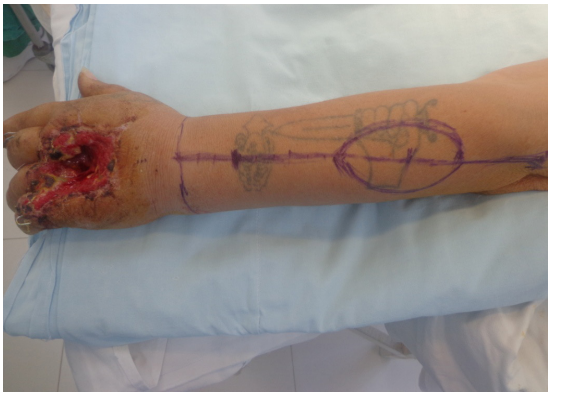
The mid pedicle length was 7.7cm.

SURGICAL CASE

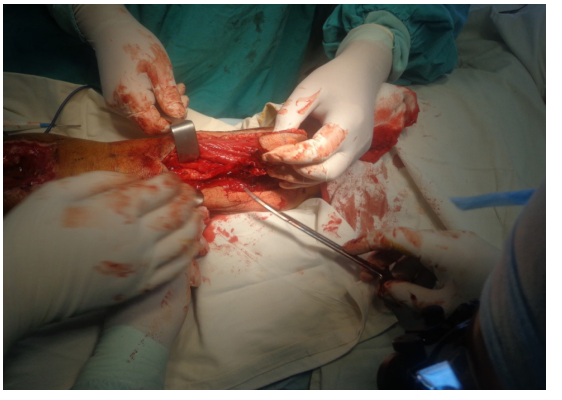
A 46 year old man with a gun related injury

Preoperative Markings

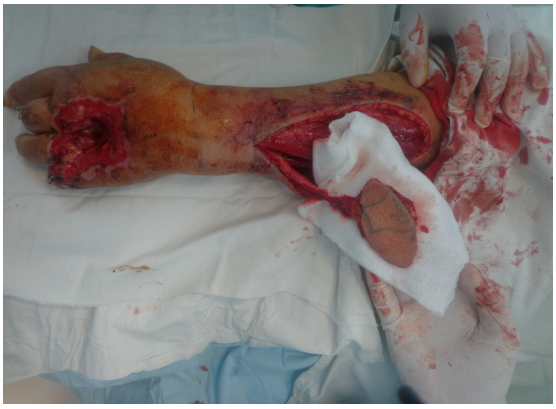


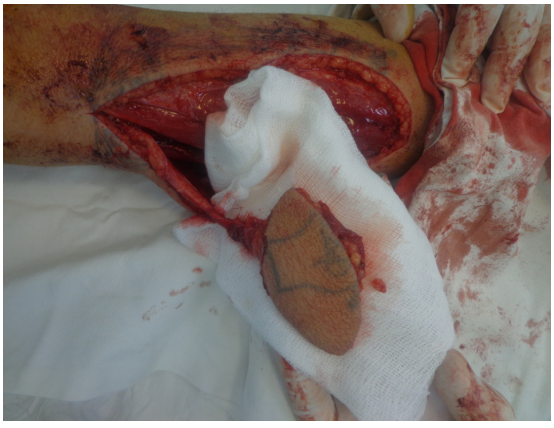


Flap Dissection

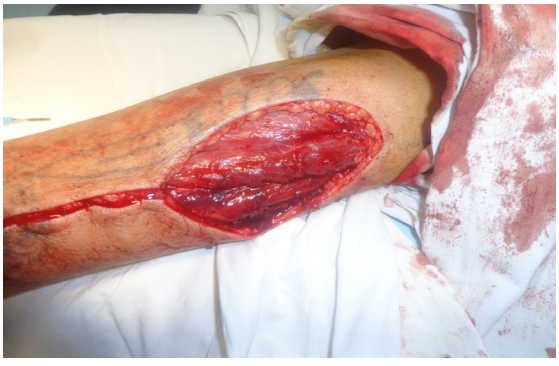


Flap Elevation

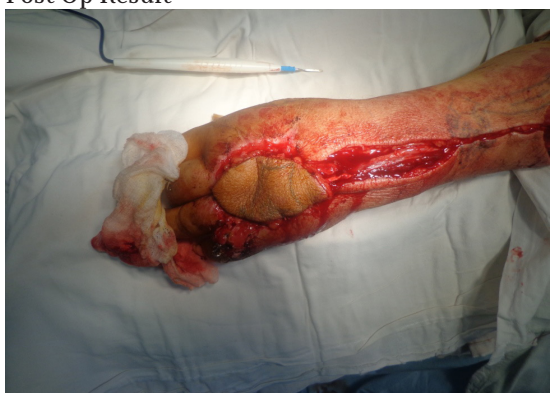




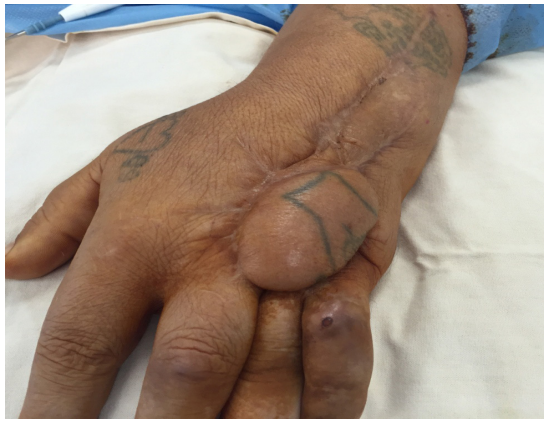
Donor Site(11x6cm)



Post Op Result



Debulking Procedure After 6 Months



CONCLUSIONS

The main advantage of the posterior interosseous flap is the location of its vascular root at the anastomosis between the posterior and the anterior interosseous arteries, making it possible to use this flap in situations where the main vascular radial or ulnar axes are damaged.

In our cases, we have found the flap particularly useful for the reconstruction of first web space contractures and large dorsal hand defects with tendon and bone exposure.

The posterior interosseous osteocutaneous flap is useful in metacarpal reconstruction and thumb reconstruction,leaving open possibilities for secondary microsurgical procedures.

The major vascular advantages of this flap are the location of the dorsal carpal anastomosis, which allows it to be used even in the presence of extensive vascular damage to the hand, and the preservation of the radial and ulnar arteries, which are the major arterial supply to the hand.

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Case report

SURGICAL TREATMENT OF GANGRENE OF THE URINE BLADDER, REVIEW OF THREE CASES

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INTRODUCTION

Gangrene of the urine bladder is very rare life threatening acute urology disease that requires extremely fast diagnoses followed by urgent and radical surgical treatment. Fronstein once noticed that gangrene of the urine bladder is so rare that should be described each appearance as a separate case. The first such case was described 1650 by Willis (1). Two etiology factors have so far been described mostly for the occurrence of the vesical gangrene. The first is the gangrenous cystitis that occurs in untreated acute cystitis in patients with reduced immunity or in female who developed gangrenous cystitis post-partum (2), and the second factor is described as a complication after embolization of the hypogastric artery or complication during pelvic thrombophlebitis (3). In the majority of cases described, surgical treatment consisted of partial or total cystectomy and temporary urinary derivation (4).

AIMS

-Analysis of the diagnosis, operative and post-operative treatment and follow-up of the patients with gangrene of the urine bladder treated at our urology department.

- Comparative analysis of the results obtained with the existing data in the world literature and relevant scientific papers regarding surgical method used for the treatment of such cases. - Determining the justification for second surgical intervention and performing definitive urinary derivation with ileal conduit.

MATERIAL AND METHODS

Three consecutive cases of vesical gangrene have been treated in the past 18 months at the

Urology Department at the General City Hospital "8th September" – Skopje, R of North Macedonia. All three were admitted as acute abdomen with septic condition and treated at the Emergency Center. Two of them were treated due to complete vesical gangrene and the third was treated first as acute abdomen caused by fibrotic obstruction of the sygma as a complication after radiaton therapy received for cervical cancer. The third case was treated for vesical gangrene developed eight months after the first surgery as a complication due to persistent recto-vesico-vaginal fistula. The patient had also ren arcuatus with bilateral uretero-hydronephrosis 2-3 degree.

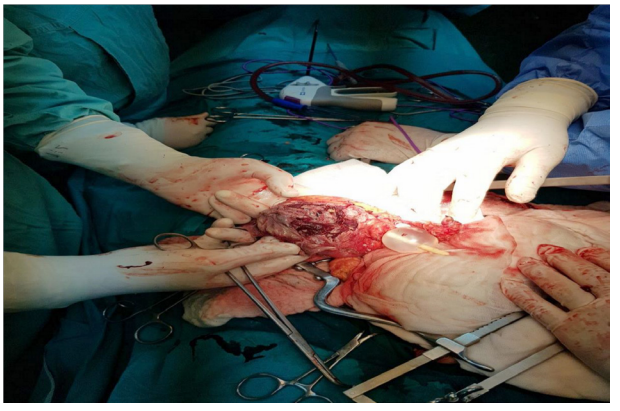
RESULTS

Clinical examination, RTG of abdomen, ultrasound, CT of abdomen, pelvic CT angiography and complete laboratory analyses were used for diagnosis and indication for urgent surgical treatment of the patients with the signs of sepsis and acute abdomen. The intraoperative finding revealed acute phlegmonoso-gangrenous peritonitis caused by complete gangrene and perforation of the urine bladder in two cases, and partial vesical gangrene with vesico-rectovaginal fistula developed eight months after partial resection and colostomy in the third case. Emergency surgery with radical cystectomy and

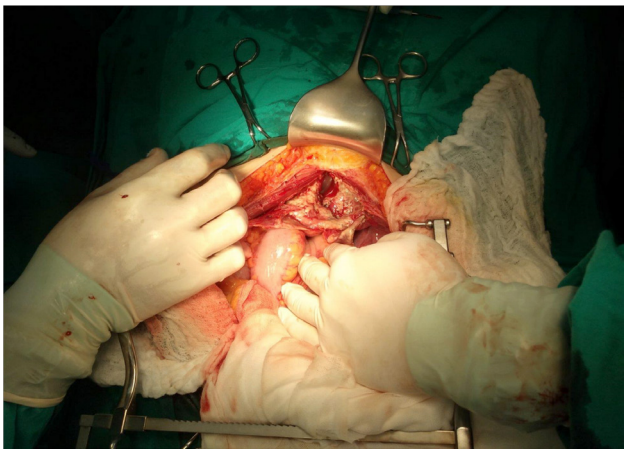
ureterocutaneostomy was performed on the patients with complete gangrene and perforation of the urine bladder. The third patient was treated as complication of persistent urinary infection due to recto-vesico-vaginal fistula and performed radical cystectomy with ileal conduit as permanent urinary derivation. Six months after the emergency surgery urinary derivation with ileal conduit was performed in one of the patients due to complete stenosis of the ureterocutaneostomy and acute obstructive renal failure with metabolic acidosis. The pathohistological findings confirmed presence of gangrene of the urine bladder wall and phlegmona of the lower part of the peritoneum. The two years' post operative follow up shows good health with normal function of the ileostoma in both patients and normal function of the ureterocutaneostoma in one patient with normal values of the electrolytes and blood degradation products.

DISCUSSION

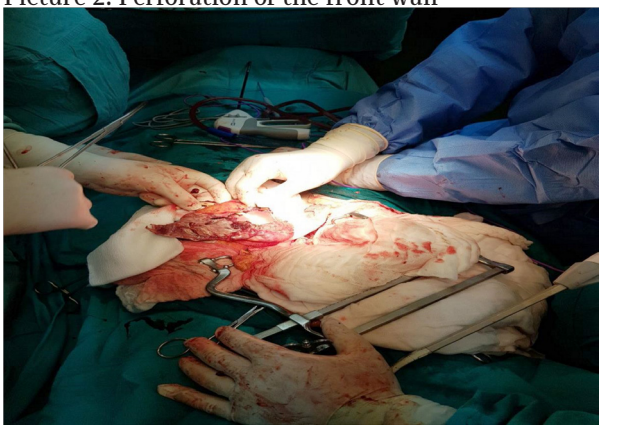
In the current literature, the etiologic factors for the occurrence of urine bladder gangrene include: urinary infections, urinary retention, colovesical fistulas (5), pelvic thrombophlebitis and recently more often iatrogenic causes such as pelvic radiation, pelvic surgery and the use of chemotherapeutic agents. In our cases the reason for vesical gangrene in two patients was acute and total occlusion of the a.iliaca interna s hypogastrica with thrombotic embolus. In first case it occurred as a result of pelvic thrombophlebitis due to hypercoagulability of the blood and cardiac arrhythmia (picture-1,2,3).



Picture 1. Complete gangrene and perforation of the urine bladder wall

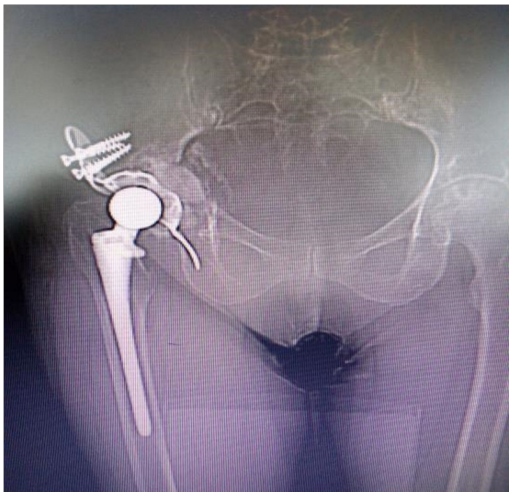


Picture 2. Perforation of the front wall

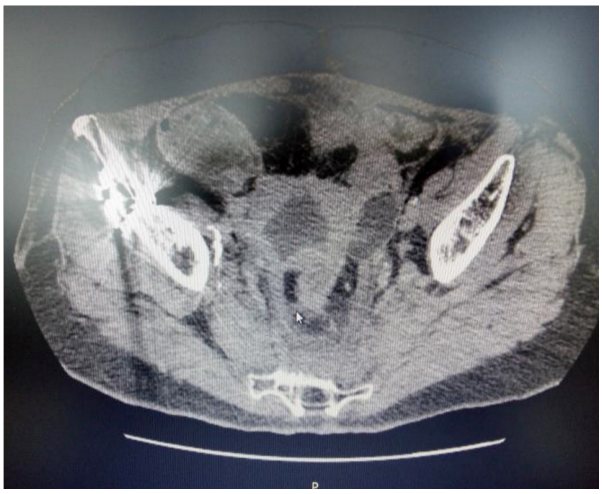


Picture 3 Gangrene of the front and upper wall with phlegmonoso-gangrenous peritonitis

In the second patient thrombembolia of the hypogastric artery occurred one week after the hip implant surgery, complicated with phlebothrombosis of the right leg and pelvis (picture 4,5).

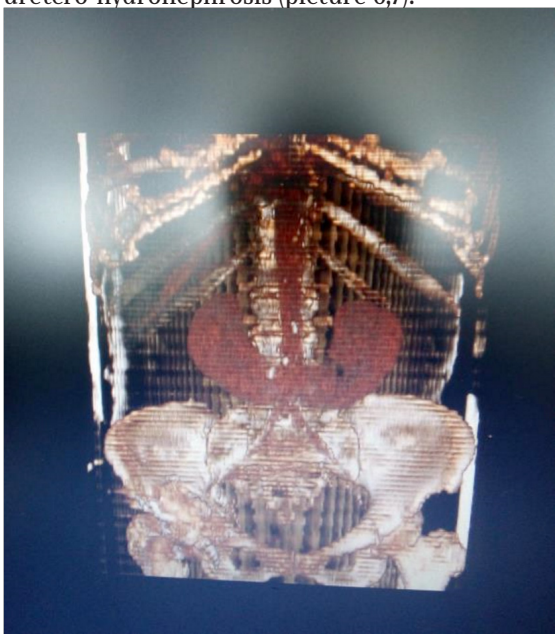


Picture 4. Right hip implant one week before the appearance of the UB gangrene

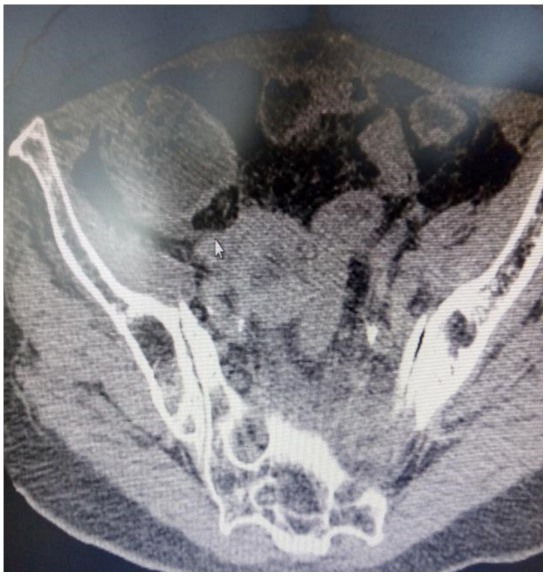


Picture 5. Gangrene of the right vesical wall

Unlike the first two cases in the third patient the vesical gangrene was caused by a prolonged bladder infection caused by the appearance of a vesico-recto-vaginal fistula. The patient also had ren arcuatus with bilateral uretero-hydronephrosis (picture 6,7).



Picture 6. Ren Arcuatus in patient with colo-vesical fistula



Picture 7 Colovesical fistula with gangrene of the left upper vesical wall

The clinical manifestation according to our described cases could be divided in two categories: acute and chronic signs and symptoms. Acute symptoms included: abdominal pain, fever, tachycardia, tachypnea, anuria, signs of ileus, laboratory signs of sepsis (high level of urea, creatinin, potassium, hepatal enzymes, hypoalbuminemia, hypoglobulinemia, leucocytemia, and high level of CRP and D-dimers). RTG of abdomen showed signs of ileus, ultrasound examination showed free liquid in the abdominal cavity and CT revealed perforation of the urine bladder. Chronic symptoms manifested in the patient with vesicovagino-rectal fistula included: continuous subfebril condition, constant suprapubic pain, constant leakage of infected urine through the vagina and rectum and secondary anemia. Retrograde vesiculography and CT urography showed presence of vesico-vagino-rectal fistula and bilateral hydronephrosis II and III stage.

CONCLUSION

Urine bladder gangrene is rare but extremely urgent life threatening condition which requires radical surgical treatment during the first 24 hours from its appearance. Acute occlusion of one of the hypogastric arteries with thromb embolus as a complication of pelvic phlebothrombosis, according to our experience is the most common cause for its appearance. Hence urgent CT of the pelvis and abdomen and pelvic CT angiography are

crucial diagnostic methods for differentiation from other causes for clinical manifestation of acute abdomen. Long presence of vesico-rectal or vesico-vagino-rectal fistula could also result with partial necrosis of the urine bladder wall, but unlike the acute occlusion of the hypogastric artery it has chronic symptoms and signs. CT urography and retrogarade urethrocystography are necessary for confirmation of the persistence of the fistulas and perforation of the urine bladder. The urgent patients with clinical symptoms and signs of acute abdomen, should be treated in two stages. The first stage should consist of radical cystectomy with bilateral ureterocutaneostomy as temporary urinary derivation. The second stage should be performed at least 2-3 months after the first surgery, where urinary diversion with ileal conduit should be performed due to the frequent occurrence of stenosis of the ureterocutaneostomas, as permanent treatment.

Key words: urine bladder gangrene, vesico-vagino-rectal fistula, pelvic phlebothrombosis, chronic cystitis, post partal cystitis.

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If a particular method used is well known then there is no need to give a complete description. You can reference the paper in

përmendni ndonjë modifikim/ndryshim që keni bërë. Jepni arsyet për përdorimin e tyre dhe vlerësoni kufizimet e tyre. Në fund, përshkruani se si i keni analizuar të dhënat tuaja, duke përfshirë metodat statistikore dhe pakon programore që keni përdorur.

Autorët e doreshkrimeve të rishqyrtuara duhet të përfshijnë një paragraf që përshkruajnë metodat që kanë përdorur për lokalizimin, përzgjedhjen, ekstrahimin dhe sintetizimin e të dhënave. Përdorni formën joveprore të foljes, në vetën e tretë, kur dokumentoni metodat, gjë që do të fokusonte vëmendjen e lexuesit tek puna që është bërë e jo tek hulumtuesi (P.sh. Janë marrë, janë realizuar, janë prezantuar etj.)

2. a) Statistikat: Përshkruani metodat statistikore me detaje të mjaftueshme për t'ia mundësuar një lexuesi me njohje në atë fushë t'i qaset të dhënave origjinale për të verifikuar rezultatet e raportuara. Kur është e mundur, përcaktoni sasinë e zbulimeve dhe prezantoni ato me indikatorë përkatës të gabimeve në matje apo pasiguri (siç janë inter-valet e besueshmërisë). Evitoni mbështetjen vetëm në testet statistikore të hipotezave, siç janë vlerat p, që dështojnë të transmetojnë informacion të rëndësishëm mbi madhësinë e efektit. Jepni detaje rreth përzgjedhjes së rasteve (randomizimi) dhe përshkruani metodat dhe sukseset e vro¬jtimit gjatë realizimit të studimeve të verbuara. Definoni termet statis¬tikore, shkurtesat dhe më së shumti simbolet. Specifikoni programin kompjuterik që është përdorur.

3. Rezultatet: Ky paragraf duhet t'i bëjë gjetjet tuaja të qarta. Prezantoni rezultatet tuaja në rend logjik në tekst, tabela dhe ilustrime, duke dhënë së pari rezultatet kryesore ose më të rëndësishme. Mos i përsërisni të gjitha të dhënat në tabela apo ilustrime, në tekst. Nënvizoni ose përm-bledhni shkurtimisht vetëm vrojtimet më të rëndësishme.

Kur të dhënat përmblidhen në paragrafin e Rezultateve, jepni rezultate numerike jo vetëm si derivate (për shembull, përqindja) por gjithashtu si numra absolut nga të cilët derivatet janë llogaritur, dhe specifikoni metodat statistikore që janë përdorur për t'i analizuar ato.

Kufizoni tabelat dhe figurat në aq sa janë të nevojshme për të sqaruar argumentin e punimit dhe për të vlerësuar të dhënat ndihmëse. Duke përdorur grafikonet për të reprezentuar të dhënat tuaja si alternativë e tabelave, do të rrisë kuptueshmërinë e lexuesit. Mos i dyfishoni të dhënat në grafikone dhe tabela. Duhet të jeni të qartë se cili lloj i grafikoneve është i përshtatshëm për informacionet tuaja. Për shembull, për të reprezentuar korelimin mes dy ndryshoreve, preferohet grafiku vijëzor, krahasuar me grafikun rrethor apo në formë shtyllash.

Sa i përket të gjitha paragrafeve, qartësia dhe të qënit i thuktë është kyçe. Mos prezantoni të njëjtat të dhëna më shumë se një herë. Kufizojeni veten në të dhënat që ndihmojnë në adresimin e hipotezave tuaja. Kjo është e rëndësishme edhe nëse të dhënat i aprovojnë ose nuk i pranojnë ato. Nëse keni bërë analiza statistikore, duhet të jepni vlerën e proba¬bilitetit (p) dhe të tregoni se është shprehës (sinjig në nivelin që ju po testoni. Varësisht nga analizat e përdorura, gjithashtu mund të jetë e rëndësishme të jepni intervalet e besueshmërisë së rezultateve (Confidence Interval –

which it was first described and mentioned any modifications you have made. Give the reasons for using them, and evaluate their limitations. Finally,, describe how you analysed your data, including the statistical methods and software package used.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data.

Use the third person passive voice when documenting methods which would focus the readers' attention on the work rather than the investigator.(e.g. Were taken, was performed, were presented itd.)

2. a) Statistics: Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as p values, which fail to convey important information about effect size. Give details about the randomization and describe the methods and success of observations while using blinded trials. Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

3. Results: This section should make your findings clear. Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text. Emphasize or summarize only the most important observations.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them.

Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Using graphs to represent your data as an alternative to tables will improve the reader's understanding. Do not duplicate data in graphs and tables. You need to be clear what type of graphs is suitable for your information. For example, to represent the correlation between two variables, a line graph is preferred to a pie chart or a bar chart.

As with all sections, clarity and conciseness is vital. Don't present the same data more than once. Restrict yourself to the data that helps to address your hypotheses. This is important whether the data supports or disproves them. If you have carried out a statistical analysis, you should give the probability (P) value and state it is significant at the level you are testing. Depending on the analysis used, it may also be important to give the confidence intervals of the results, or the statistical parameters such as the odds ratios. Provide a caption for each figure making the gen¬eral meaning clear without reference to the main text, but don't discuss the results. Let the readers decide for themselves what they think of the data. Your chance to say what you think comes next, in the discussion.

3. Tables: Each table should be inserted at the point of the text where they have to be placed logically, typed by the same rules

CI), ose parametrat statistikorë si proporcionet e rastit (odds ratio). Bëni përshkrimin tek secila figurë duke bërë të qartë domethënien e përgjithshme pa referencë në tekstin kryesorë, por mos diskutoni rezultatet në të. Lëreni lexuesin të vendosë vetë se çfarë men-don për të dhënat. Mundësia juaj për të thënë se çfarë mendoni, është në vazhdim, tek diskutimi.

3. Tabelat: Secila tabelë duhet të vendoset në vendin e tekstit ku duhet të vihet logjikisht, e plotësuar me të njëjtat rregulla sikur teksti i plotë. Mos i dërgoni tabelat si fotografi. Secila tabelë duhet të citohet në tekst. Tabelat duhet të jenë me numra ashtu që të jenë në koordinim me refer-encat e cituara në tekst. Shkruani një përshkrim të shkurtë të tabelës nën titullin. Çdo sqarim shtesë, legjendë ose sqarim i shkurtesave jostan¬darde, duhet të vendoset menjëherë poshtë tabelës.

4. Diskutimi: Ky paragraf është pjesa ku ju mund të interpretoni të dhë-nat tuaja dhe të diskutoni duke ballafaquar dhe krahasuar gjetjet tuaja me ato të hulumtuesve të mëparshëm. Rishikoni referencat e literaturës dhe shihni nëse mund të përfundoni se si të dhënat tuaja përkojnë me atë që keni gjetur.

Ju gjithashtu duhet të llogarisni rezultatet, duke u fokusuar në mekaniz¬mat në prapavij të vrojtimit. Diskutoni nëse rezultatet tuaja mbështesin hipotezat tuaja origjinale. Gjetjet negative janë aq të rëndësishme në zhvillimin e ideve të ardhshme sikur gjetjet pozitive.

E rëndësishme është se, nuk ka rezultate të këqija. Shkenca nuk të bëjë me të drejtën dhe të gabuarën, por merret me zgjerimin e njohjeve të reja.

Diskutoni si janë paraqitur gabimet në studimin tuaj dhe çfarë hapa keni ndërmarrë për të minimizuar ato, kështu duke treguar se ju çmoni ku¬fizimet e punës tuaj dhe fuqinë e përfundimeve tuaja. Duhet gjithashtu të merrni në konsideratë ndërlikimet e gjetjeve për hulumtimet në të ardhmen dhe për praktikën klinike. Lidhni përfundimet me qëllimet e studimit, por evitoni qëndrimet dhe përfundimet e pakualifikuara, që nuk mbështeten në mënyrë adekuate nga të dhënat. Shmangni prioritetet deklarative apo të aludoni në punën që nuk është krahasuar.

5. Referencimi: Referencat janë baza mbi të cilën është ndërtuar raporti juaj. Shqyrtimi i literaturës dhe leximi i referencave gjithmonë duhet të jetë pikë fillestare e projektit tuaj. Ky paragraf duhet të jetë i saktë dhe të përfshijë të gjitha burimet e informacionit që keni përdorur.

Në formatin " Vancouver" , referencat numërohen një nga një, sikur që shfaqen në tekst dhe identifikohen me numra në bibliografi..

Shënoni të gjithë autorët kur janë gjashtë e më pak; kur janë shtatë ose më tepër, shënoni tre të parët, pastaj shtoni "et.al." Pas emrave të autorëve shkruhet titulli i artikullit; emri i revistës i shkurtuar sipas mënyrës së Index Medicus; viti i botimit; numri i vëllimit; dhe numri i faqes së parë dhe të fundit.

Referencat e librave duhet të jepen sipas emrit të autorit, titulli i librit (mund të citohet edhe titulli i kapitullit para titullit), vendi i botimit, botuesi dhe viti.

as for the full text. Do not send tables as photographs. Each table should be cited in the text.Tables should be numbered so that they will be in sequence with references cited in the text. Provide a brief explanation of the table below the title. Any additional explanations, legends or explanations of non¬standard abbreviations, should be placed immediately below the table.

4. Discussion: This section is where you interpret your data and discuss how your findings compare with those of previous researchers. Go over the references of your literature review and see if you can determine how your data fits with what you have found.

You also need to account for the results, focusing on the mechanisms be¬hind the observation. Discuss whether or not your results support your original hypotheses. Negative findings are just as important to the de¬velopment of future ideas as the positive ones.

Importantly, there are not bad results. Science is not about right or wrong but about the continuing development of knowledge.

Discuss how errors may have been introduced into your study and what steps you took to minimise them, thus showing that you appreciate the limitations of your work and the strength of your conclusions. You should also consider the implications of the findings for future research and for clinical practice. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. Avoid claiming priority or alluding to work that has not been compared.

5. Referencing: The references are the foundation on which your report is built. Literature searches and reading of references should always be the starting point of your project. This section must be accurate and in¬clude all the sources of information you used.

In the Vancouver format, references are numbered consecutively as they appear in the text and are identified in the bibliography by numerals.

List all authors when there are six or fewer; when there are seven or more, list the first three, then add "et al." The authors' namer are fol-lowed by the title of the article; the title of the journal abbreviated ac-cording to the style of Index Medicus; the year of publication; the volume number; and the first and last page numbers.

References to books should give the names of any editors, place of publication, editor, and year.

In the text, reference numbers are given in superscript. Notice that issue number is omitted if there is continuous pagination through¬out a volume, there is space between volume number and page numbers, page numbers are in elided form (51-4 rather than 51-54) and the name of journal or book is in italics.The following is a sample reference:

Në tekst, numrat e referencave jepen me indeks të sipërm. Vëreni se çështja e numrave neglizhohet nëse ka numërtim të vazhdueshëm përg¬jatë gjithë vëllimit, ka hapësirë mes numrit të vëllimit dhe numrit të faqes, numrat e faqeve janë në këtë formë: 51-4 në vend të 51-54, dhe emri i revistës ose librit është në italic. Në vazhdim është një shembull i referencës:

Artikujt e revistave:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. *N Engl J Med* 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. *BMJ* 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. *Lancet* 1997;349: 1498-504.

Librat dhe tekste tjera:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. *National service framework for coronary heart disease*. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Kamberi A, Kondili A, Goda A, dhe bp; *Udhërrëfyes i shkurtër i Shoqatës Shqiptare të Kardiologjisë për parandalimin e Sëmundjes Aterosklerotike Kardiovaskulare në praktikën klinike*, Tiranë, 2006
7. Azemi M, Shala M, dhe bp. *Pediatria sociale dhe mbrojtja shëndetësore e fëmijëve dhe nënave*. Pediatria, Prishtinë 2010; 9-25

Shmangni përdorimin e abstrakteve si referenca; "të dhëna të papub-likuara" dhe "komunikime personale". Referencat e pranueshme, por ende të papublikuara lejohet të merren, vetëm nëse shënoni se janë "në shtyp".

6. Mirënjohjet: Ju mund të keni dëshirë të falënderoni njerëzit që ju kanë ndihmuar. Këto mund të rangohen prej atyre që ju kanë përkrahur me teknika eksperimentale deri tek ata që ju kanë këshilluar deri në bër¬jen e dorëshkrimit final.

7. Formati i fajllit të të dhënave për **ilustrimet** (**figurat**): JPG

Nëse përdoren fotografitë e pacientëve, qoftë subjekti, qoftë fotografitë e tyre nuk duhet të jenë të identifikuara, ato duhet të shoqërohen me lejen e shkruar nga ta për përdorimin e figurës. Format e lejuara janë në dispozicion nga redaksia.

Nëse fajllet e të dhënave janë shumë të mëdha për t'u dërguar me e-mail, rekomandohet dërgimi me CD në adresën tonë.

8. Legjendat për Ilustrimet (Figurat)

Legjenda e tabelës duhet të vendoset mbi tabelë. Referenca e një tabeleje, e cila është marrë nga ndonjë publikim tjetër, duhet të vendoset poshtë tabelës. (Është përgjegjësi e autorit të sigurojë lejen e ribotimit nga botuesit e atij botimi) Legjenda e figurës duhet të vendoset në fund të faqes. Referenca e figurës e marrë nga ndonjë tjetër publikim vendoset në fund të legjendës. (Leja e ribotimit duhet të sigurohet nga botuesi i këtij botimi).

Journal articles:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. *N Engl J Med* 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. *BMJ* 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet 1997;349: 1498-504.

Books and other monographs:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. *National service framework for coronary heart disease*. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Osler AG. *Complement: mechanisms and functions*. Englewood Cliffs: Prentice-Hall, 1976.

Avoid using as references abstracts; "unpublished data" and "personal communications". References to accepted but yet unpublished articles are allowed to be made, only if you note "in press".

6. Acknowledgements: You may wish to acknowledge people who have helped you. These can range from those who supported you with exper¬imental techniques to those who read or offered advice on your final manuscript.

7. Data file format for **illustrations** (**figures**): JPG

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permis-sion to use the figure. Permission forms are available from the Editor.

If data files are too big for transmission as an Email attachment submis¬sion of a CD to our address is recommended.

8. Legends for Illustrations (Figures)

The legend of a table has to be placed above the table. The reference of a table, which has been taken from another publication, must be placed below the table. (It is the author's responsibility to obtain the permission of reproduction from the publishers of the publication.) Figure legends are to be placed at the end of the paper. The reference of a figure taken from another publication stands at the end of the legend. (Permission of reproduction must be obtained from the publishers of this publication).