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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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BODY FAT DISTRIBUTION CHANGES DURING WEIGHT LOSS DETERMINED BY DUAL-ENERGY X-RAY ABSORPTIOMETRIC TRUNK/ TOTAL RATIOS AS INDEXES OF ABDOMINAL OBESITY

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ABSTRACT

Objective. The effect of weight loss on body fat distribution was examined through the trunk/total tissue and fat mass ratios, indexes of central, abdominal obesity determined by dual-energy X-ray absorptiometry (DXA).

Material and methods. Following parameters were determined before and after weight loss: body mass index (BMI), body weight (BW), total and trunk fat mass (FM) and its percent (FM%), tissue mass (TM) and TM fat percent (TMf%) with DXA as well as DXA indexes of abdominal body fat distribution: trunk/total FM (Tr/To FM) and Tr/To FM%, trunk/total TM (Tr/To TM) and trunk/total TMf% (Tr/To TMf%) in two overweight subjects.

Results. BW of 62.9±1.2 kg and BMI value of 28.98±0.78 kg/m2 before the weight loss lowered to 49.96±1.3 kg ($p<0.012$) and normal BMI 22.81±0.62 kg/m2 ($p<0.012$). Tr/To TMf% value decrease from 1.02±0.01 to 0.97±0.03 was significant ($p<0.013$) and Tr/To FM% value decrease from 1.04±0.01 to 0.99±0.02 was also significant ($p<0.01$). Tr/To TM value decreased significantly from 0.55±0.02 to normal value 0.48±0.02 ($p<0.019$). Tr/To FM index value decreased significantly from 0.56±0.02 to normal value 0.48±0.03 ($p<0.033$). Tr/To TM and Tr/To FM after weight loss reached normal values.

Conclusions. It was confirmed that DXA indexes of central, abdominal obesity Tr/To TM and Tr/To FM were increased in overweight subjects before the weight loss and lowered significantly after the weight loss to normal values, indicating that normal BMI and BW reached after the weight loss were associated with normalized body fat distribution.

Key words: dual-energy x-rays absorptiometry, abdominal obesity, weight loss

INTRODUCTION

Obesity is a medical condition in which excess body fat has accumulated to an extent that it may have a negative effect on health [1]. Obesity and central body fat distribution are known risk factors for cardiovascular and metabolic diseases. Excess abdominal fat is referred to as android obesity and it is an important, independent risk factor for disease, which is associated with increased risk for cardiovascular disease. Android obesity, which is predominantly visceral, intra-abdominal, is more predictive of adipose-related comorbidities than gynecoid obesity, which has a relatively peripheral (gluteal) distribution. In a previous study, in 2011 Shubeska S. [2] discovered with DXA that BMI increase in healthy women was associated with a more pronounced abdominal body

fat distribution [3]. DXA enabled precise, accurate body composition and body fat distribution assessment and showed that BMI increase was associated with more pronounced abdominal obesity, indicating substantially higher risk for development of metabolic and cardiovascular complications of the hyperinsulinemic-dyslipidemic syndrome [2]. DXA is an excellent method to measure and monitor body composition changes in obese patients undergoing weight loss. DXA can precisely monitor how much fat was lost during weight loss.

Some relationship ratios between central (android, abdominal) regional tissue and FM to peripheral gynoid regional parts of the body in patients with Cushing's syndrome (CS) were discovered as diagnostic criteria of visceral, abdominal obesity in patients with CS [4, 5]. DXA indexes of central, abdominal obesity trunk/total TM and FM and trunk/total TMf% and FM% ratios discovered extreme central body fat distribution in CS, differentiated them significantly from healthy women with normal BMI and obese with the same BMI as CS, and are discovered DXA indexes of abdominal, central obesity that should be used as DXA indexes of extreme central, abdominal obesity in CS and non CS obese women. They are indicators of abdominal obesity [5, 6]. DXA body composition and fat distribution assessment may be useful in studies related to obesity-associated risks [7, 8].

The aim of this study was to investigate body composition and body fat distribution with DXA indexes of central, abdominal obesity, trunk/total TM and trunk/total FM, as well as trunk/total TMf% and trunk/total FM% and their changes after weight loss with consequent normal BMI and BW. It was important to discover weight loss influence on body fat distribution.

MATERIAL AND METHODS

BMI, and BW reduction were determined in two overweight postmenopausal (postMP) women before and after weight loss, as well as total (To) and trunk (Tr) fat mass (FM) and its percent (FM%), tissue mass (TM) and TM fat percent (TMf%) and the changes of the DXA indexes of abdominal body fat distribution Tr/To FM and Tr/To FM%, Tr/To TM and Tr/To TMf%. BW and BMI values reduction during weight loss were significant ($p<0.012$), and are shown on Table 1.

Table1. BMI and BW values before and after weight loss

	Before weight lost	After weight lost	P
BMI (kg/m2)	28.98±0.78	22.81±0.62	0.012
Body weight (kg)	62.96±1.2	49.96±1.3	0.012

BMI – body mass index

Body height was measured by a wall stadiometer in barefoot subjects with head in a horizontal Frankfurt plane to the nearest 0.1 cm. BW was measured by a digital scale while wearing light clothing and it was estimated in kilograms (kg). BMI was calculated with the following formula: weight (kg)/height (m2). DXA assessment was performed with DXA System Lunar DPX-NT, which uses encore 10.x Windows-XP Professional OS computers. The entire body of the subject was scanned. During DXA scan, the subject was in a supine position while the x-ray scanner performed a series of transverse scans, measured at 1-cm intervals from the top of the head to the bottom of the toes. The DXA machine was calibrated daily in accordance with the manufacturer's guidelines to ensure adequate quality control. The system enabled simultaneous assessment of total and regional body composition and body fat distribution.

Statistical analyses were performed using the statistical software program SPSS for Windows, version 19. Differences between the examined values before and after the weight loss were tested by One-Sample T Test. P values <0.05 were considered to be statistically significant.

RESULTS

Table 1. Tr/To TM, Tr/To TMf%, Tr/To FM and Tr/To FM% values before and after weight loss

	Before weight lost	After weight lost	P
Trunk/Total TM	0.55±0.02	0.48±0.02	0.019
Trunk/Total Tf%	1.02±0.01	0.97±0.03	0.013
Trunk/Total FM	0.56±0.02	0.48±0.03	0.033
Trunk/Total FM%	1.04±0.01	0.99±0.02	0.01

TM – tissue mass FM – fat mass
TMf% - tissue mass fat percent FM% – fat mass percent

Tr/To TM value higher than cut-off point value of 0.52 before the weight loss indicated visceral body fat distribution. Mean Tr/To TM value of 0.55 before weight loss lowered significantly to mean value of 0.48 that is a normal value ($p<0.019$).

Tr/To FM cut-off point value of 0.56 before the weight loss

indicated visceral body fat distribution. Tr/To FM index value decrease from 0.56±0.02 to normal value 0.48±0.03 was also significant ($p<0.033$).

Trunk/Total TMf% and Trunk/Total FM% also lowered significantly after the weight loss ($p<0.013$; $p<0.01$). Tr/To TM, Tr/To TMf%, Tr/To FM and Tr/To FM% values before and after the weight loss are shown in Table 2.

DISCUSSION

Obese subjects have higher percentage of FM from the total body mass compared to non obese. Central obesity can be an early warning sign of a condition called metabolic syndrome. The core abnormality of Metabolic Syndrome is the increased body weight, and particularly central, abdominal obesity as well as dyslipidemia. People with metabolic syndrome have elevated blood pressure, high triglycerides, low levels of HDL cholesterol and insulin resistance. This combination of factors creates an especially high risk for stroke, coronary artery disease, cardiovascular disease-related mortality and type 2 diabetes. DXA measurements of fat distribution may be useful in studies related to obesity-associated disease risk [3, 9]. There is a growing evidence that intra-abdominal adipose tissue (IAAT), rather than total body fat, is a risk factor for metabolic conditions associated with obesity. For this reason, the evaluation of IAAT is clinically important [10]. It was discovered with DXA that BMI increase in healthy women was associated with a more pronounced abdominal fat distribution [2, 3]. Because of that, effective methods for assessing visceral fat are important to investigate its role for the increased health risks in obesity [9]. There is an increased interest in the evaluation of various methods for assessment of body composition and fat distribution [11].

Menopause is a high-risk time for weight gain. PostMP women have significantly more fat, a more central fat distribution, and less lean tissue mass than premenopausal (preMP) women [12, 13]. Menopause-related central body fat accumulation potentially contributes to the increased incidence of disease observed in postMP, compared with preMP women [14, 15]. The subjects in this study were postmenopausal.

DXA method determines absolute (kg) and relative (%) total, bone, lean and fat body mass and separately their regional values on arms, legs, head and trunk. Body composition, including fat mass, body fat distribution and muscle mass, gradually change with aging, even if the body weight and BMI remain unchanged. LBM decreases significantly, while fat mass increases and is preferentially stored in abdominal tissues [16, 17, 18]. Trunk FM increase is a result of dominant android, abdominal FM increase indicating increased risk for metabolic complications [6]. Body fat distribution is simply determined with DXA by the relationship of the regional (segmental) fat compartments. The relationship of the predominantly central, android, abdominal FM and tissue mass (TM) and the gynoid (peripheral FM and TM) is an indicator of the central, abdominal obesity [4]. DXA is fast becoming the new "gold" standard" because it provides a higher degree of precision in only one measurement and has the ability to show exactly where fat is distributed throughout the body. It's a very reliable method and its results are extremely repeatable; in addition, the method is safe and presents little burden to the subject.

It was found that low weight, independent of menopausal status, leads to the typical gynoid pattern of fat distribution while excess weight and obesity result in an android pattern of distribution in pre- and postMP women [7]. By measuring body composition, a person's health status can be more accurately assessed and the effects of both dietary and physical activity programs better directed. Since, a scale measures "body weight," which includes fat, muscles, bones and organs, it can't specifically tell how much fat had been lost, and the only way to measure actual fat loss is to measure "body composition," not body weight in weight loss programs. DXA can precisely monitor how much fat is lost during weight loss [19, 20].

Total body analysis with DXA is the ideal way for the serious athlete, the person monitoring or beginning a program of exercise or weight loss, or anyone curious or concerned about their health to receive a quick, painless, accurate and confidential assessment of their body's composition. Also, measurements of body composition and body fat distribution with DXA have provided a research tool to study the metabolic effects of aging, obesity, and various wasting conditions.

Changes in body composition during weight loss programs might have a significant effect on long-term results and sensitive DXA indexes of abdominal, central obesity are needed, because of lack of normal reference data, which is an issue that is currently being addressed.

CS patients are a discovered gold standard of extreme central, visceral, abdominal body fat distribution. DXA

indexes of central, abdominal body fat distribution in Cushing's (CS) could also be used as a gold standard for abdominal obesity in non CS. They were discovered as a diagnostic criterion of extreme central, visceral obesity in CS. Shubeska-Stratrova S. (2015) [4], showed that the ratios of insignificantly different central and peripheral regional parts of the body, precisely differentiated the patients with CS and non CS obese (non CS) with the same BMI as CS (CO), and confirmed central body fat distribution in CS [12, 20, 21]. In that study it was found that DXA indexes trunk/total TM and trunk/total FM ratios differentiated CS and CO with very high significance ($p<0.001$), and discovered extreme central body fat distribution in CS. They differentiated CS patients significantly from healthy non obese women (C) and CO, and could be used as DXA indexes of extreme central, abdominal obesity in CS and non CS abdominal obese women. DXA indexes of central body fat distribution in CS could also be a gold standard and diagnostic criterion of extreme central, abdominal fat distribution in different types of obesity (non CS).

Cut-off points of the following indexes confirmed extreme central, abdominal obesity: trunk/total TM ratio higher than 0.52 and trunk/total FM ratio higher than 0.54 [4, 12]. Normal cut-off point values were discovered, trunk/total TM value lower than 0.51 and trunk total FM value lower than 0.52. Tr/To TM index cut-off point value of 0.51 differentiated CS patients and C with normal BMI and body fat distribution with sensitivity, specificity, postitive and negative predictive and diagnostic value of 100%. Tr/To FM index cut-off point value of 0.52 differentiated CS patients and C with normal BMI and body fat distribution with sensitivity and negative predictive value of 100%, specificity of 83.3%, postitive predictive value of 85.71% and diagnostic value of 91.67%.

In this study, mean Tr/To TM ratio value of 0.55 was higher than normal cut-off point value of 0.51, which confirmed abdominal body mass distribution, and it reduced to normal mean value of 0.48 indicating normal body fat distribution. Also, mean Tr/To FM ratio value of 0.56 was equal with cut-off point value of extreme central, abdominal obesity, and it reduced to normal mean value of 0.48 indicating normal body fat distribution. Tr/To TM reduction during weight loss was significant ($p<0.019$), as well as Tr/To FM reduction ($p<0.033$). Trunk/Total TMf% and Trunk/Total FM% also lowered significantly after weight loss ($p<0.013$; $p<0.01$). Significant reduction in these indexes of central obesity after the weight loss confirmed reduction of abdominal obesity and normalized body fat distribution.

CONCLUSION

It can be concluded that trunk/total tissue mass and trunk/total fat mass ratios values before the weight loss confirmed abdominal obesity indicating higher cardiovascular risk in DXA examined overweight subjects. Significant reduction in BMI, BW and these indexes of central obesity, trunk/total tissue mass ratio and trunk/total fat mass ratio, trunk/total TMf% and trunk/total FM% and their change to normal levels after the weight loss, confirmed reduction of abdominal obesity and consecutive normalized body composition and body fat distribution. This showed that body weight reduction in overweight subjects and especially in obese subjects is important in order to improve body composition and body fat distribution and minimize the cardiometabolic profile and risk. These results confirmed that DXA measurements of body composition and body fat distribution are very useful in studies related to obesity-associated disease risk. Tr/To TMf% and Tr/To FM% are also useful indexes in body fat distribution assessment. This study confirmed that these indexes Tr/To TM and Tr/To FM are worthwhile, diagnostic procedure parameters of abdominal obesity and obesity associated risks.

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Original scientific paper

ASSOCIATION OF THE APOE GENE POLYMORPHISM WITH DIABETIC NEPHROPATHY

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ABSTRACT

The protein isoformes that are products of the Apolipoprotein E (APOB) gene polymorphism have partially altered biological activity and that may lead to greater susceptibility of the patients to microvascular complications including Diabetic nephropathy (DN) in patients with the Type 2 diabetes mellitus (T2DM). The aim of this study was to evaluate the association between the allele ε2, ε3, and ε4 of the APOE gene, as well as their combination, with the development of DN in patients with T2DM from the North Macedonia. The genotypic and allele frequency of the polymorphisms rs429358 and rs7412 in the APOE gene was determined in a group of patients with T2DM (with and without DN), and in the control group healthy subjects. The study is designed as a case-control genetic association study. The samples from 88 patients with T2DM were analyzed, including 57 patients with DN and 31 without DN and 26 healthy controls. The demographic, clinical and laboratory data were analyzed in addition to the genetic profiling of the patients.

Genotyping of the APOE gene polymorphism resulted in determination of the patient's genotype: ε2/ε2, ε3/ε3, ε4/ε4, ε2/ε3, ε2/ε4 or ε3/ε4, as well as of the alleles: ε2, ε3 or ε4. The results revealed a statistically significant association of the genotype ε2/ε3 (p=0.016) and the allele ε2 (p=0.020) with the occurrence of DN compared to the other genotypes and alleles. The presence of this genotype increases the chances of DN by 4,24 folds and the relative risk by 1,50 folds. In conclusion, the correlation of the APOE gene polymorphism and the development of the DN in patients with T2DM was confirmed indicating that there is a potential applicable value in the prognosis and treatment selection.

Keywords: APOB; polymorphisms; Type 2 Diabetes mellitus; Diabetic nephropathy.

INTRODUCTION

The type 2 Diabetes mellitus (T2DM) patients suffer wide range of additional multi organ complications that largely influence their quality of life. The pathogenesis of most of the complications is often not completely clarified and the genetic predisposition can be considered an important risk factor. One of the most serious microvascular complication of T2DM found in 20 to 40% of patients is Diabetic nephropathy (DN) causing chronic renal insufficiency (1, 2). Since it is a disease that is multifactorialy influenced, the genetic factor cannot be excluded.

The APOE gene, located on chromosome 19, is considered to play a main role in the lipid metabolism and transport since it encodes for apolipoprotein E. Apolipoprotein E has numerous functions in the transportation of chylomicrons, cholesterol, and other important metabolic lipid pathways and has been associated with the pathophysiology of dyslipidemias in carriers of certain genotypes. In terms of the polymorphism of this gene, there are three most common alleles: ε2, ε3 and ε4. Therefore, the resulting six possible genotypes in the

population are: ε2ε2, ε3ε3, ε4ε4, ε2ε3, ε2ε4 and ε3ε4. The protein isoformes that are products of some of the genotypes have partially altered biological activity and that may lead to greater susceptibility of the patients to microvascular complications involving a range of clinical entities, including DN.

The aim of this study was to evaluate the association between the allele ε2, ε3, and ε4 of the APOE gene, as well as their combination, with the development of diabetic nephropathy in patients with type 2 diabetes from the Republic of North Macedonia. More closely, the genotypic and allele frequency of the polymorphisms rs429358 and rs7412 in the APOE gene was determined in a group of patients with type 2 diabetes (with and without nephropathy), and in the control group healthy subjects. The association might help in reduction of DN by prevention.

MATERIALS AND METHODS

This study is prospective, observational and genetic-associated. The demographic, clinical, laboratory and genetic data was gathered from a group of about 100 patients with type 2 diabetes, of which a subgroup of 57 patients is with nephropathy and a subgroup of 31 patients are without nephropathy. Patients were selected to have had diabetes for a similar period of time. For the patients with type 2 diabetes, the basic criteria were: HbA1c≥6.5 mmol/L and under an oral antidiabetic therapy or with insulin. For the diabetic nephropathy, the basic criteria were: microalbuminuria 30-300 mg / 24 h (initial phase), or microalbuminuria> 300 mg / 24 h (advanced phase). The 26 control subjects were healthy blood donors and volunteers who do not have anamnestic, clinical and laboratory signs of diabetes, nor for kidney disease, nor have family history.

Samples of less than 3 mL venous blood with anticoagulant (EDTA.Na2) were collected after a signed consent of each patient was provided, as well as with the approval of the Ethics Committee. The isolation of genomic DNA was by the method of Gemmell and Akiyama (3). Molecular analyzes were performed by genotyping using TaqMan fluorescent probes with a nucleotide sequence that is specific to the amplified region of the respective gene, labeled at the 5'-end with the FAM or VIC fluorescent reporter dyes, while at the 3'-end with the non fluorescent quencher NFQ. The polymorphisms rs429358 and rs7412 and therefore the presence of alleles Ɛ2, Ɛ2, and Ɛ2 of the APOE gene was based on fluorescence genotyping with the qRT-PCR system (4,5).

The statistical and population-genetic calculations were performed using RealStatistics 2015 and GenAlEx 6.5, installed on Microsoft Excel 2016. The relationship of diabetic nephropathy in patients with type 2 diabetes was compared with the frequencies of genotypes and alleles of polymorphism tested with Pearson's Chi-square test and with the Fisher Exact Test as well as with the Cochran-Armitage Trend test. The normal distribution was determined by the Shapiro-Wilk test. Furthermore, the two-way Student's t-test and the Mann-Whitney U-test were used in case of deviations from the normal distribution of the values of the corresponding parameter. The probability index or odds ratio was also calculated. The confidence interval (CI) was calculated at 95%, respectively, with $p < 0.05$. For the estimation of eligibility of the group of the analyzed patients for population-genetic studies the Hardy-Weinberg's equilibrium, rate of genetic diversity and heterozygosity rate were calculated.

RESULTS

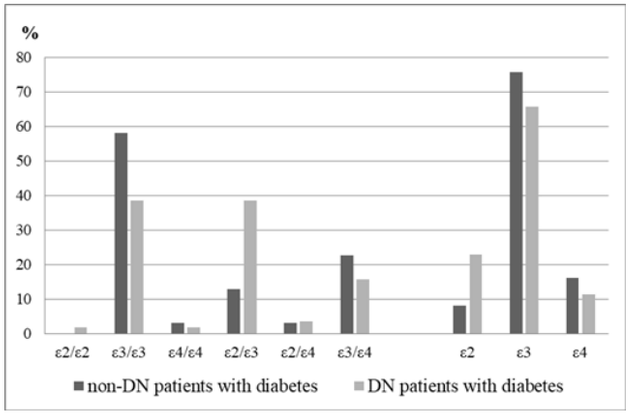
The basic demographic, clinical and laboratory parameters for the group of the patients with type 2 diabetes with and without nephropathy are shown in Table 1.

Table 1. Demographic. clinical and laboratory data of the patients

Parametar	All patients with T2DM n=88 (100%)	T2DM with DN n=57 (64,77%)	T2DM without DN n=31(35,22%)
Male, n (%)	48 (54,54)	36 (63,16)	12 (38,71)
Female, n (%)	40 (45,45)	21 (36,84)	19 (61,29)
Age (years ± SD*)	49,73 ±8,21	49,88 ±8,60	49,59 ±7,82
BMI when diagnosed with T2DM (n ± SD)	29,365 ±3,75	30,28 ±4,66	28,45 ±2,85
Systolic artery pressure (mmHg ± SD)	132,47 ±17,67	137,02 ±19,91	127,93 ±15,44
Diastolic artery pressure (mmHg ± SD)	83,755 ± 8,53	85,44 ±9,32	82,07 ±7,74
HbA1c (mmol/L ± SD)	8,8 ±1,68	8,98 ±1,93	8,63 ±1,43
Total Cholesterol mmol/L	4,72 ± 1,18	4,78 ±1,27	4,66 ±1,10
HDL-C	1,02 ± 0,265	0,96 ±0,17	1,08 ± 0,36

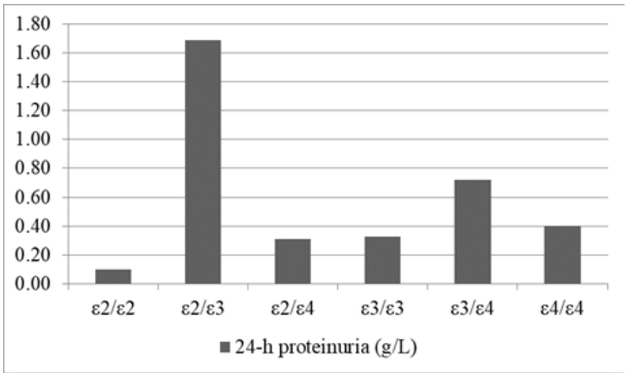
*SD = standard deviation

Genotyping of the APOE gene polymorphism resulted in determination of the patient's genotype: ε2/ε2, ε3/ε3, ε4/ε4, ε2/ε3, ε2/ε4 or ε3/ε4, as well as of the alleles: ε2, ε3 or ε4. The results revealed a statistically significant association of the genotype ε2/ε3 (p=0.016) and the allele ε2 (p=0.020) with the occurrence of nephropathy compared to the other genotypes and alleles (Graph 1).



Graph 1. Differences in genotypes and alleles frequencies between the non-DN and DN patients with diabetes. Bars represent the percentage of patients with the genotype

From the patients with diabetic nephropathy, the 24 hour proteinuria values were significantly higher in the patients with the genotype ε2/ε3 (p<0,0001) (Graph 1).



Graph 2. Differences in the values of 24-h proteinuria in the DN patients with diabetes.

The results from the genetic analysis showed a statistically significant association of genotype ε2/ε3 with the occurrence of nephropathy. The presence of this genotype increases the chances of developing nephropathy by 4,24 folds and the relative risk by 1,50 folds (Table 2.)

Table 2. Applicability of the APOE polymorphism as a potential predictive biomarker for development of DN in patients with T2DM

Statistic parameter	Value	Lower bound (95%)	Upper bound (95%)
Sensitivity, %	38,60	27,09	51,60
Specificity, %	87,10	70,37	95,34
Positive Predictive Value (PPV)	0,85	0,71	0,98
Negative Predictive Value (NPV)	0,44	0,31	0,56
Relative risk, folds	1,50	1,15	1,96
Odds ratio, folds	4,24	1,37	13,11

DISCUSSION

Type 2 Diabetes mellitus with all the accompanying complications is a disease with a pronounced familial predisposition which confirms the genetic factor. People who have a positive history of DT2 in first-degree relatives have a greater risk of DT2. The environmental factors also play a crucial role in the development of DT2. An abundant calorie diet, high glucose intake and sedentary lifestyle are among the first most challenging factors in the onset of the disease (6,7). Therefore, the combination of the genetic predispiosition and the environmental factors may lead to early development of DT2.

The genetic association of certain gene polymorphisms with the development of T2DM has been extensively studied over the past twenty years. Integrative approaches derived from genetic research at the level of genomic, transcriptional, epigenetic, proteomic and other levels have also been published in recent years (8). With the application of genome-wide associative studies by examining the connection of single nucleotide polymorphisms, over 100 gene loci have been found to be considered to play a role in the development of the disease.

Although the number of studies of the APOE gene polymorphism is not as high, it is a subject to intense research since it was found that it can be considered a prognostic and risk factor for other complications of diabetes such as cardiovascular disease, cerebrovascular and ischemic infarcts, retinopathy, and others. The polymorphism of the APOE gene is a candidate genetic marker for the development of DN. In most references, the frequencies of allele Ɛ2 and the genotype Ɛ2 / Ɛ3 are

significantly higher in patients with DN while the alele ε3 and the ε3 / ε3 genotype were found to be renoprotectve (9). According to the results of the Japanese study of Araki et al. (10) allele ε2 is designated as a prognostic risk factor for the development of DN in patients with DT2. Early determination of the risk for diabetic nephropathy may give an opportunity for taking preventive and therapeutic measures resulting in possible delay of this complication.

In conclusion, the detection of the APOE polymorphism in patients with DT2 can help in prediction of the development of the complication and such patients are candidates for appropriate renoprotective medicaments in combination with more frequent controls and certain dietary and lifestyle recommendations.

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Original scientific paper

HOMOCYSTINEMIA AND POLYMORPHYSM OF THE GENE FOR METHYLENTETRAHYDROFOLATE REDUCTASE (C677T) IN PATIENT WITH CORONARY ARTERY DISEASE

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ABSTRACT

Background: Hyperhomocysteinaemia either due to mutation of the enzyme methylentetrahydrofolate reductase (MTHFR) gene or deficiency of vitamin B12 and folic acid, has been reported as a risk factor for coronary artery disease (CAD). The aim of this study was to determine the concentration of total homocysteine (tHcy) and prevalence of C677T mutation of methylentetrahydrofolate reductase (MTHFR) in healthy subjects and in patients with coronary artery disease (CAD). Also, to evaluate the concentration of tHcy and to analyse if might this mutation will use for prediction of diagnosis of this disease.

Material and methods: The investigation comprised 123 healthy subjects control, and 81 consecutive angiography confirmed CAD patients. The concentration of plasma tHcy was determined by cyclical enzymatic method and the MTHFR gene polymorphism was analyzed by the polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP).

Results: The concentration of plasma tHcy in healthy subjects was statistically significant lower compared with patients with CAD, $p<0.001$. The highest frequency of mutation of MTFHR gene C677T, was found for genotype CT, then follows wild genotype CC and the lowest frequency of genotype TT in control and CAD groups.

Conclusions: The results have shown that plasma tHcy levels is a contributing factor for development of this disease CAD . Influence of polymorphysm of MTHFR gene in the examined alleles and their combinations in genotypes on occurrence of CAD was not statistically significant.
Key words: total homocysteine, coronary artery disease, methylentetrahydrofolate reductase

INTRODUCTION:

In spite of the large number of epidemiological data about the association of hyperhomocysteinemia and artery thrombosis, little is known about the pathophysiology. A spectrum of mechanisms have been involved in the occurrence of artery thrombosis. Some of them also participate in the occurrence of vascular diseases 1,2. Coronary artery disease (CAD) is the consequence of atherosclerotic plaque disposition on the coronary artery wall. High levels of total homocystein (tHcy), hyperhomocysteinemia have been identified as a risk factor for atherosclerosis3. The mechanism for the vascular lesions induced by hyperhomocysteinemia remains unclear. Experimental evidence suggests that Hcy facilitates the vascular oxidative process, thereby altering the coagulation system, and reduces the vasomotor regulation of the endothelium4.

More recently, interest in the role of the genetic factor in the occurrence of moderate hyperchomocysteinemia has increased. Its manifestation depends on interactions

between environmental and genetic risk factors. Individual susceptibility to the disease has been associated with functional allelic variation. Thus, the identification of gene polymorphisms relating to the formation of atherosclerotic plaques, and consequently, thrombi, may contribute towards developing early diagnostic methods and guiding preventive procedures5. The latest investigations have demonstrated that the gene responsible for MTHFR polymorphism is localized at chromosome 1p 36.3 and it is composed of 11 exons and 10 introns. Codon 677 of MTHFR gene on exon 4 is responsible for hyperhomocysteinemia 6,7. The common CƐT change in the sequence of the genetic code in MTHFR enzyme is at nucleotide 677 and the mutation results in substitution of alanine by valine at position 222 of the polypeptide 7,8. Mutation of C677T gene might influence composition of intracellular folate pool, and therefore, the homozygous form of this mutation and the heterozygous one in a lesser degree is associated with an increased Hcy concentration and a low folate status 7,9.

The aim of this study was to determine the concentration tHcy and prevalence of C677T mutation, of MTHFR in healthy subjects, control and in patients with CAD and to evaluate might this mutation will use for prediction of diagnosis of CAD.

MATERIAL AND METHODS

The investigation comprised 204 subjects divided into two groups.

1. Healthy subjects (control group), n = 123

2. Patients with coronary artery diseases, n = 81

1.The control group of subjects was consisted of blood donors from the Institute of Transfusion Medicine in R of Macedonia, who were declared to be healthy by a medical doctor. Exclusion criteria in the control group included positive family history for hereditary disease associated with impaired homocysteine metabolism as well as diseases that were also known to be associated with impaired homocysteine metabolism.

2.Coronary artery disease in patients was diagnosed by ultrasonography and/or coronarography at the Clinic of Cardiology, Medical faculty, Skopje, R of Macedonia. Exclusion criteria in this group of patients was positive family history for hereditary diseases associated with impaired homocysteine metabolism, diabetes mellitus, cerebrovascular insult, autoimmune diseases (systemic lupus erythematodes), severe form of psoriasis, all types of carcinoma, kidney failure and transplantation, thyroid gland diseases, usage of hypolipidemics and vitamin B6, B12 and folic acid.

All patients and healthy inviduals included in this study signed a written consent to participate in the study which was approved by the Committee of the Ministry of Education and Science from the Republc of Macedonia (No. 13-1672/4-02).

Several days prior to blood analyses, each respondent got specific instructions: to avoid protein-rich food or fatty food 24 hours prior examination. Blood samples were drawn from antecubital vein in the morning, after 10-12 hours fast. Concentration of serum tHcy was determined by cyclic enzymatic method at the Institute of Medical and Experimental Biochemistry, Medical Faculty in Skopje. The assay method was based on enzymatic conversion of homocysteine to S-adenosyl homocysteine, followed by quantification of S-adenosyl-L-homocysteine by glutamate dehydrogenase . NADH like coenzyme transform into NAD+ and this is manifested as decline apsorbancy to 340 nm 10.

Genetic polymorphism of C677T in MTHFR enzyme was analyzed by polymerase chain reaction by Schneider 11, at the Institute of Molecular Biology and Human Genetics at the Faculty of Natural and Mathematical Sciences in Skopje. Isolation of genomic DNA from nucleic cells (leukocytes) was done with sodium chloride - extraction and subsequent precipitation with ethanol, amplification of regions of MTHFR gene was done by polymerase chain reaction and detection of CƐT missense mutation in C677T in MTHFR gene was made by restriction analysis (Polymerase Chain Reaction-Restriction Fragment Lenght Polymorphism - PCR-RFLP),Figure 1

STATISTICAL METHODS

Genotype and allele frequencies in CAD and control groups were compared by Chi square testing. The characteristics of patients and controls were evaluated by comparing biochemical findings using the Student t-test. Additionally, we performed multiple logistic regression model testing on the interaction of genotype and the total Hcy levels as a known risk factors. (*All analyses were performed using SPSS v.11.5 (SPSS Inc., Chicago, USA) statistical analysis software.) A two-tailed p value of $p < 0.05$ was considered statistically significant.

RESULTS

The results of concentraton of serum total homocysteine in both investigated groups are presented on Table 1. Patients with CAD had significantly higher levels of tHcy compared with control group, p<0.001.

In both groups, the highest frequency in the healthy subjects and patients the mutations in the MTFHR gene had C677T, heterozyguos genotype CT in (46% vs 50 %), of homozygous wild genotype CC (44% vs 33%) and the lowest frequency has the of genotype TT with (10% vs 17%) Table 2.

Comparison of tHcy plasma concentrations with a specific C677T polymorphism genotype in the MTHFR gene in all of examined groups is shown in Table 3. The lowest concentrations of tHcy were obtained in both investigated groups with genotype CC, higher in the heterozygous CT genotype, and the highest in those with a variant genotype TT individuals,. Analysis of the differences have shown that statistically significant were only among the genotypes CC and CT in the control group (p <0.05). Differences in concentrations relative to the genotypes of the both analyzed groups were not statistically significant (p> 0.05).

The statistical comparison of the wild-type allele C allele with those of the variant T and genotype the wild type CC with those of the heterozygous CT or homozygous variant TT of the MTHFR C677T polymorphism of the control group in relation to examined group of patients with CAD is shown in Table 4. From the table it can be concluded that, the presence of either of the two alleles C or T does not have a significant correlation with the risk of CAD in relation to a control.,healty group Namely, none of the p-values calculated according to the two types of analyzes from the group of x2 tests, nor did they show statistically significance (p> 0.05) according to Fischer's test. Similarly, there is no connection either between the presence of the wild type genotype CC, nor the CT and TT genotypes containing the variant allele, with the examined group of patients with CAD. Although with greater variations, additional statistical analysis of the probability ratio OR, risk ratio RR, and confidence interval (95% CI) confirmed the absence of association of these genetic parameters with the group of patients with CAD.

From all this it follows that the risk of CAD does not differ significantly in persons with examined alleles and their combinations into the genotypes.

DISCUSSION

The levels obtained for total plasma homocysteine were significantly higher in patients with coronary artery disease in comparison with the control group, p<0.001. Our data are in compliance with observations from a number of other studies in which they confirmed that hyperhomocysteinemia, even moderate, is a independed factor for development of coronary artery disease 12-16.

The assotiation between higher risk of CAD in individuals with hyperhomocysteinemia, so it is still unclear questionable.17.

The polymorphism of the MTHFR gene C677T is responsible in most cases for mild to moderate hyperhomocysteinemia and is one of the rare genetic risk factors proven today. Our findings have shown statistically differences in the healthy subjects, control group between the lowest homocysteine concentration in individuals with the genotype CC with higher in those with the heterozygous CT genotype and with the highest in those with the variant TT genotype, p<0.05. This fact proves that the mutation of the MTHFR gene C677T may affect the composition of the intracellular folate capacity (pool), which is involved in methabolism of homocysteine, so that the homozygous of this mutation, and to a lesser extent the heterozygous, is accompanied by an increased concentration of tHcy18-20. In this sense, it has been proven that folic acid stabilizes and preserves the function of the mutated enzyme, a fact that will be the basis for the eventual treatment of hyperhomocysteinemia 20,21.

The MTHFR genotypes C677T in control group are associated with the level of tHcy. . The presence of either of the two alleles C or T does not have a significant correlation with the risk of CAD in relation to a healthy, control group. Namely, in the group of CAD none of the p-values calculated according to the two types of analyzes from the group of x2 tests, nor even according to the Fisher test, show statistical significance p>0.05. Similarly, there is no connection either between the presence of the wild type genotype CC, nor the CT and TT genotypes containing the variant allele, with the examined group of patients with the CAD. Although with higher variations, additional statistical evidence of the absence of association of these genetic parameters with the tested group is obtained with the values of the probability ratio (OR), the risk ratio (RR), and the confidence interval (95% CI) 19,22 .

Naghshtabrizi et all, show that there is compliance

with most published papers that the risk for CAD is related to the genotypes CT and TT and that there is a statistically significant difference between moderate hyperhocysteinemia and these genotypes 23. Some studies, performed in patients with CAD, confirm our understanding that hyperhomocysteinemia is a fact for development of this disease, but it is not statistically significant in the examined alleles and their combinations in genotypes ($p > 0.05$) 24.

There are also other risk factors wich increased the additional risk for development the CAD beside hyperhomocysteinemia, there is a search for new such as lipoprotein (a), fibrinogen, C-reactive protein, because only with the classic conventional risk factors it is not possible 25.

In our study, the average homocysteine level was significanty higher in the patient group than the control. This is in agreement with observations by other investigatiors.

Also, our findings present mutations in the gene MTHFR C677T are not single factors for development of CAD, but they have influence on tHcy levels. The proven is that the coronary artery disease is a complex disorder where environmental and genetic markers both play an important role.

Acknowledgements

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Table1. The concentrations of the tHcy (mmol/L) in control and patients with CAD

tHcy µmol/L $\overline{X} \pm SD$	N	Control group	N	Patients with CAD	p
	123	9,7±3,65	81	16±5,93	p<0.001

The results are expressed with mean ± standard deviation, p statistically significance

Table2: The frequencies of polymorphism of MTHFR gene C677T in both groups

Genotype	Control (%) N=123	CAD(%) N=81	p
CC	44	33	<0.05
CT	46	50	<0.05
TT	10	17	<0.05

p, statistical significance;

Table 3. Comparison of tHcy concentration (mmol/L) with the MTHFR C677T polymorphism genotype in control and CAD group

Genotype	Control group tHcy (µmol/L) N=123	Group of CAD tHcy (µmol/L) N=81
CC	9,32 ± 1,83	16,28 ± 4,94
CT	12,24 ± 2,82	19,81 ± 5,28
TT	14,70 ± 5,54	20,62 ± 4,96
CC and CT	p = 0,001	p = 0,054
CC and TT	p = 0,146	p = 0,104
CT and TT	p = 0,444	p = 0,734

The results are expressed with mean ± standard deviation, p statistically significance

198bp

175bp

Table 4. Comparison of the frequencies of the allele and genotypes of the MTHFR C677T polymorphism in the control over the CAD group

Parameters	Control (N=123)	CAD (N= 81)	x2-test Yates P	x2-test Pearson p	Fisher P	OR	RR	95%CI
Alel								
C	174	102	0.301;	0.232	0.261	1.472	0.825	0.781-2.775
T	72	60	0.301;	0.232	0.261	0.680	1.212	0.360-1.281
Genotype								
CC	60	8	0.351;	0.249	0.274	1.677	0.763	0.695-4.046
CT/TT	63	53	0.351;	0.249	0.274	0.569	1.311	0.247-1.439

* The statistical significance is calculated according to the x2 test with Yates correction and according to Pearson.
**Fisher's Exact Test for Probability Two-way distribution; OR, Odds Ratio; RR, Risk Ratio; CI, confidence Interval at 95%

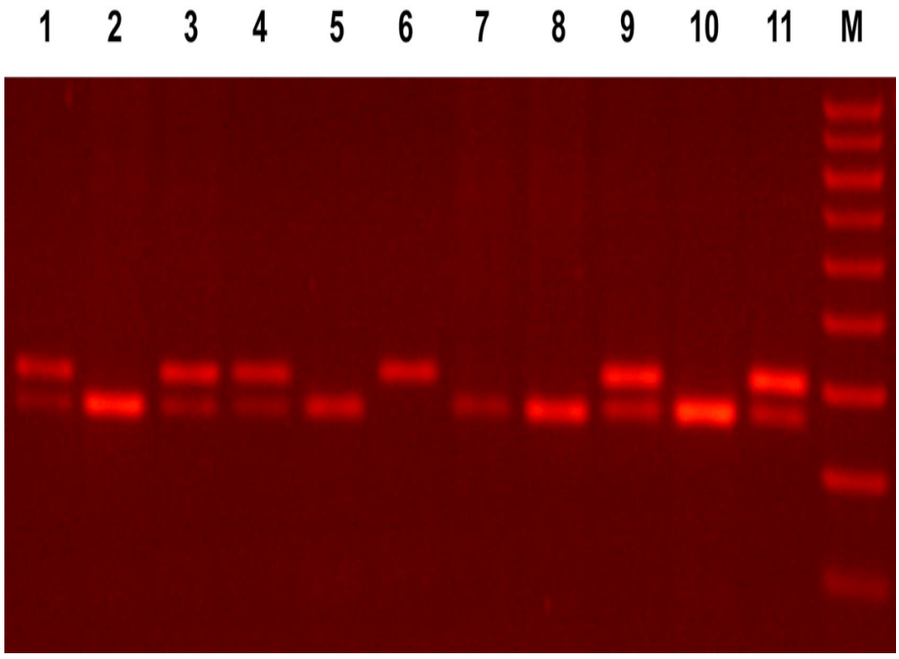

Figure 1

Detection of MTHFR polymorphism. On lane 6 there is wild type (CC) genotype, on lanes 1, 3, 4, 9 and 11 there are mutant heterozygous (CT) genotype and on lines 2,5,7,8 and 10 mutant homozygous (TT) genotype; M, molecular weight marker

Original scientific paper

„ЕР, ПР И КИ-67 КАЈ ПРИМАРЕН КАРЦИНОМ НА ДОЈКА И КАЈ МЕТАСТАЗИ ВО АКСИЛАРНИТЕ ЛИМФНИ ЈАЗЛИ“.

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АПСТРАКТ

Вовед : Карцином на дојка е еден малигнен тумор многу чест кај жените и еден од водечките причинители за смртност од малигни заболувања кај жените во светот. Молекуларните биомаркери како што се Естрогенот и Прогестеронот, имаат значајна улога во третманот на пациенти кои имаат корист од ендокрина терапија. Неодамна и Ки-67 е рапортиран за да биде не само прогностички фактор, туку и како еден важен маркер во апликацијата на адјувантна терапија. Важен одлучувачки фактор за терапевтската стратегија е присуството на метастази, особено во регионалните лимфни јазли, затоа важно е да се испита молекуларниот профил на метастазите, бидејќи некои податоци укажуваат на нестабилност на рецепторите на туморските клетки во текот на метастатскиот процес.

Цел : Да се проучат хормонските рецептори и Ки-67 со имунохистохемиска метода кај инвазивниот рак на дојка, и да се спореди експресијата на ЕР, ПР и Ки-67 помеѓу примарниот тумор и метастатскиот тумор во аксиларните лимфни јазли.

Дизајн : Испитувањето е ретроспективно-проспективно.

Материјал и методи: Во истражувањето беа вклучени 30 испитанички, пациентки со инвазивен рак на дојка и со метастази во аксиларните лимфни јазли. Субјектите кои беа вклучени во истражувањето, беа подложни на радикална мастектомија и аксијална дисекција. Направена е анализа на имунохистохемиските боења на ткивото од примарниот карцином и на ткивото од метастатскиот депозит во аксиларните лимфни јали. Имунохистохемијата за Ер, Пр и Кі-67 рецепторите беше применета според протоколите на производителот. (En vision+, DAKO Denmark).

Резултати : Ова испитување е спроведено на ткивото на триесетте пациенти-жени на возраст од 33 - 75 години. Туморот со градиус 2 доминираше кај 63.3% (19 жени). Градус 1 не е најден кај ниту еден случај, додека со градус 3 беа пронајдени 36.7%(11 жени). ЕР-позитивни примарни тумори беа 76.7%, додека ЕР-позитивни метастатски тумори во аксиларните лимфни јазли беа 70%. Стапката на совпаѓање беше 66.7%, додека стапката на несовпаѓање беше 33.3%. ПР-позитивни примарни тумори беа 70%, додека ПР-позитивни метастатски тумори во аксиларните лимфни јазли беа 63.3%. Стапката на совпаѓање беше 73.3%, додека стапката на несовпаѓање беше 26.7%. Експресијата на Ки-67 беше детектирана кај 80% примарни инвазивни карциноми на дојка, и кај 76.7% метастатски тумори во аксиларните лимфни јазли. Стапката на совпаѓање беше 83.3%, додека стапката на несовпаѓање беше 16.7%.

Заклучок : Во нашата студија нема значајна разлика за ЕР,ПР и Ки-67 рецепторите, помеѓу примарниот тумор и метастазите во аксиларни лимфни јазли, меѓутоа во оваа студија се забележува дека степенот на совпаѓање за ЕР и ПР во овие две локации за рак на дојка не е премногу висока, и недостаток на сигнификанца во овој аспект би межел да биде поради малиот број на примероци.Високото присуство на несовпаѓање (иако несигнификантно во моментов) на ЕР и ПР рецептори помеѓу примарниот тумор на дојка и во аксиларните метастази, не дозволува можност да се сугерира дека експресијата на една локација за ЕР и ПР да важи подеднакво и на другата локација.

Клучни зборови : естроген, прогестерон, ки-67, рецептор, карцином

ВОВЕД

Карцином на дојка е еден малигнен тумор многу чест кај жените, и ако што се расте во еден експониран орган, кој има лесен пристап за самоегзаминирање и клиничко дијагдостицирање. Ова неоплазма е голем проблем и еден од водечките причинители за смртност од малигни заболувања кај жените во светот (1,2,3)

Ова неоплазма се опишува како хетерогена променлива болест, како во клиничкиот така и во патолошкиот аспект, но исто така и одговорот на терапијата и прогнозата се различни.(4,5,6)

Ризичните фактори за појава на рак на дојка се утврдени: возраст, пол, репродуктивните фактори, хормоналната нерамнотежа, диета, и како многу честа појава покажува поврзаноста со семејството, каде што се идентификуваат две гени (БРЦА1 и БРЦА2), кои значително го зголемуваат ризикот од рак на дојка. (7)

Инвазивниот дуктален карцином, претставува најголема група на инвазивен рак на дојка. Инвазивниот карцином на дојка е група на епителијални малигни тумори кои се карактеризираат со инвазија на околното ткиво и е со изразена тенденција за метастази, каде почесто се сретнуваат аксиларни лимфни јазли, кои во исто време претставуваат значаен прогностички фактор. (7, 8, 9)

Пријавени се многу основни туморски биомаркери за подобро препознавање на туморогенезата на карцином на дојка, прогресија на болеста, инструкции за лекување, како и за прогностички и предвидливи цели. (3,10)

Традиционалните биомаркери како што се Естроген (ЕР) и Прогестерон (ПР) не се само клинички прогностички фактори, туку исто така имат сигнификанта улога на селектирање на пациенти кои би имале бенефит од ендокрина терапија. (3, 8, 10)

Ки-67 е биомаркер на клеточната пролиферација сто е изразено(експресира) во јадрото на клетките во фазите на клеточниот циклус(G1, S, M). Неодамна и Ки-67 е рапортиран за да биде не само прогностички фактор, туку и како еден важен маркер на апликацијата на адјувантна терапија. (11)

Класичниот хистопатолошки преглед за прогноза и третман на пациентите вклучува : големина на туморот, хистолошки подтип, степен на диференцијација, метастази во лимфните јазли, лимфоваскуларна инвазија, експресија на ЕР и ПР рецептор, прекумерна експресија на Хер-2/неу и индекс на пролиферација преку Ки-67.Овие податоци се добиени од внимателните патолошки анализи во примероците од пациентите со карцином на дојка. (3,8,10,12,13,14,15,16)

Важен одлучувачки фактор за терапевтската стратегија, која ќе го одреди идниот исход кај пациентите, е присуството на метастази, особено во регионалните лимфни јазли. Денес, важно е да се испита молекуларниот профил на метастази, бидејќи некои податоци укажуваат на нестабилност на рецепторите на туморските клетки во текот на метастатскиот процес (6,17,18,19,20,21)

ЦЕЛ НА ИСПИТУВАЊЕТО

1. Да се испита и спореди експресијата на ЕР, ПР и Ki-67, помеѓу примарниот и метастатичкиот тумор во аксиларните лимфни јазли кај инвазивен дуктален карцином на дојка.

МАТЕРИЈАЛ И МЕТОДИ

Ова проучување вклучува триесет пациенти, дијагностицирани со инвазивен карцином на дојка, преку хистопатолошко испитување извршено во Универзитетскиот Клинички Центар во Косово.

Сите пациенти кои беа вклучени во проучувањето имаа метастази во аксиларните лимфни јазли. Пациентите биле подложни на радикална мастектомија и аксиларна дисекција. Сите пациенти кои беа избрани во студијата, не беа подложени на претходна терапија.

Испитувањето е ретроспективно-проспективно, кое се реализира со парафински блокови и примероци на нови пациенти. Пациентите кои беа испитувани беа на возраст од 33-75 години, а испитувањето беше одобрена од Комитетот за Етика на Медицинскиот Факултет на Универзитетската Клиника во Косово.

Имунохистохемијата на мануален начин беше применета како метод. Имунохистохемијата за ЕР, ПР и Ki-67 рецепторите беше применета според протоколите на производителот. (En vision+, DAKO Denmark).

Сечените туморални ткива 3-4 микрони, се депарафинираат преку топлина од 60*C за еден час, потоа се потопуваат во чист ксилол два пати од по 15 минути, продолжувајќи на етанол со различни проценти(99%, 95% и 70%) и завршувајќи во дестилирана вода.

Детектирање на антигенот се изврши со буфер (ph 9.0 или ph 6.0) и со затоплување на садот за испарување (олоку 95°C).

После блокирање на ендогената пероксидаза, ткивата се инкубираат со примарно антитело за 30 минути потоа се врши исплакнување со Трис буфер за 10 минути, се аплицира секундарното антитело за 30 минути, потоа се исплакнува со Трис буфер, се аплицира хромогена субстанца (ДАБ) за 10 минути, па повторно исплакнување со дестилирана вода за 5 минути. Сечењата се бојадисуваат со хематоксилин за една минута, кои се исплакнуваат со течна вода, потоа се дехидрираат во алкохол на тој начин зголемувајќи ја концентацијата (70%, 95% и 99%). По исплакнувањето во клилол се покриваат со покривно стакло и се готови за микроскопско изгледувањае.

МИКРОСКОПСКА ЕВАЛУАЦИЈА

Интерпретацијата на ЕР и ПР имунохистохемијата се изведува според упатствата на Американското Здружение за Клиничка Онкологија (ASCO). (22) Резултатите за ЕР и ПР експресија се одредуват како: 0, +, ++ и +++.

0 (негативо) нема нуклеарно боење

+ (позитивно) нуклеарното боење е 0-25%

++ (позитивно) нуклеарното боење е 26-50%

+++ (позитивно) нуклеарното боење е над 50%

Интерпретацијата на индекс на пролиферација се мери преку Ки-67, која се изведува од оценување на процентот на клетките, со боење на јадрото во полињата со повисока митотична активност.(23)

За маркерот Ки-67 го употребивме границата 14%, како лимит за дефинирање на случаите висока/ниска.(24)

РЕЗУЛТАТИ

Во истражувањето беа вклучени 30 испитанички, пациентки со инвазивен рак на дојка и со метастази во аксиларните лимфни јазли. Пациентките беа на просечна возраст од 55.33 ± 12.3 години, најмладата пациентка имаше 33 години, најстарата беше на 75 годишна возраст.(Таб 2)

Десностранa локализација на заболување имаа 43.3% (13 жени), со левостранa локализација беа 56.7% (17 жени).(Таб 1)

Тумор со градиус 2 доминираше кај 63.3% (19 жени). (Таб 1)

Табела 1 Локализација и градус на тумор

Варијабла	n (%)
Локализација	
Десно	13 (43.33)
Лево	17 (56.67)
Градус	
2	19 (63.33)
3	11 (36.67)

Табела 2 Возраст на пациентки и големина на туморот

Варијабла	mean ± SD	min-max	median
возраст	55.33 ± 12.3	33 – 75	
големина на туморот (cm)	3.39 ± 1.98	1.3 – 11.5	2.5

Во согласност со резултатите од табела 3, ЕР-позитивни примарни тумори беа 76.7% (n=23), додека ЕР-позитивни метастатски тумори во аксиларните лимфни јазли беа 70% (n=21). Стапката на совпаѓање беше 66.7% (n=20), додека стапката на несовпаѓање беше 33.3% (n=10). Меѓу нив, 20% (n=6) пациентки имаа ЕР-позитивен примарен тумор, но ЕР-негативен метастатски, и 13.3% (n=4) пациентки имаа ЕР-негативен примарен тумор, но ЕР-позитивен метастатски тумор.

Карра коефициентот имаше вредност од 0.153, што укажува на слабо совпаѓање во експресијата на ЕР рецепторот помеѓу примарниот инвазивен дуктален карцином на дојка и метастазите во лимфните аксиларни јазли.

Статистичката анализа за компарацијата на експресијата на овој маркер меѓу примарниот и метастатскиот тумор во аксиларните лимфни јазли кај инвазивен карцином на дојка, не потврди статистички сигнификантна разлика (p=0.56).

Табела 3 Експресија на ЕР рецепторот помеѓу примарниот и метастатичкиот тумор на дојка

Примарен тумор на дојка	Метастатичкиот тумор на дојка		N	Карра	T	p-level
	ЕР позитив	ЕР негатив				
ЕР позитивни	17	6	23	0.153	0.848	0.397
ЕР негативни	4	3	7			
Вкупно	21	9	30			

Chi-square = 0.34 p=0.56

Резултатите од табела 4 покажуваат дека ПР-позитивни примарни тумори беа 70% (n=21), додека ПР-позитивни метастатски тумори во аксиларните лимфни јазли беа 63.3% (n=19). Стапката на совпаѓање беше 73.3% (n=22), додека стапката на несовпаѓање беше 26.7% (n=8). Меѓу нив, 16,7% (n=5) пациентки имаа ПР-позитивен примарен тумор, но ПР-негативен метастатски, и 10% (n=3) пациентки имаа ПР-негативен примарен тумор, но ПР-позитивен метастатски тумор.

Карра коефициентот имаше вредност од 0.403, што укажува на средна јачина на совпаѓање во експресијата на ПР рецепторот помеѓу примарниот инвазивен карцином на дојка и метастазите во лимфните аксиларни јазли.

Не се потврди статистичка сигнификантна разлика во експресијата на овој маркер меѓу примарниот и метастатскиот тумор во аксиларните лимфни јазли кај инвазивен карцином на дојка (p=0.58).

Табела 4 Експресија на ПР рецепторот помеѓу примарниот и метастатичкиот тумор на дојка

Примарен тумор на дојка	Метастатичкиот тумор на дојка		N	Карра	T	p-level
	ПР позитив	ПР негатив				
ПР позитивни	16	5	21	0.403	2.232	0.026 sig
ПР нагативни	3	6	9			
Вкупно	19	11	30			

Chi-square = 0.3 p=0.58

Согласно резултатите од табела 5 експресија на Ки-67 беше детектирана кај 80% (n=24) примарни инвазивни карциноми на дојка, и кај 76.7% (n=23) метастатски тумори во аксиларните лимфни јазли . Стапката на совпаѓање беше 83.3% (n=25), додека стапката на несовпаѓање беше 16.7% (n=5).Меѓу нив, 10% (n=3) пациентки имаа висока пролиферација на Ки- 67 кај примарен тумор, но ниска Ки-67 кај метастази, и 6.7% (n=2) пациентки имаа ниска пролиферација на Ки-67 кај примарен тумор, но висока пролиферација на Ки-67 во метастатски тумор.

Карра коефициентот имаше вредност од 0.51, што укажува на средна јачина на совпаѓање во експресијата на Ки-67 рецепторот помеѓу примарниот инвазивен карцином на дојка и метастазите во лимфните аксиларни јазли.

Статистичи несигнификантна беше разликата во експресијата на Ки-67 рецепторот меѓу примарниот и метастатскиот тумор во аксиларните лимфни јазли кај инвазивен дуктален карцином на дојка (p=0.58).

Табела 5 Експресија на Ки-67 рецепторот помеѓу примарниот и метастатичкиот тумор

Примарен тумор на дојка	Метастатичкиот тумор на дојка		N	Карра	T	p-level
	Ки-67 висока	Ки-67 ниска				
Ки-67 висока	21	3	24	0.510	2.806	0.005 sig
Ки-67 ниска	2	4	6			
Вкупно	23	7	30			

Chi-square = 0.1 p=0.75

СТАТИСТИЧКА АНАЛИЗА

За статистичка обработка на податоците, добиени во текот на истражувањето беше направена база во статистичкиот програм SPSS for Windows 23,0.

За одредување на степенот на совпаѓање во експресијата на анализираните хормонски рецептори беше користен Карра тестот.

Споредбата на статусот на овие маркери меѓу примарниот и метастатски инвазивен карцином на дојка беше анализирана со Chi-square test).

За статистички сигнификантни беа земени вредностите на $p<0.05$.

ДИСКУСИЈА

Ракот на дојката е најчестата неоплазма со висок степен на смртност. Овој рак освен степенот и стадиумот, на рутински начин се вреднува и со статусот на хормонските рецептори (ЕР и ПР) и експресија на Ки-67, преку имунохистохемиски методи со цел да доаѓаме до точната дијагноза, и за да се избере соодветна терапија. (2, 24).

Нашата цел беше да ги употребиме имунохистохемиските методи за да го идентификуваме статусот на хормонските рецептори и експресијата на Ки-67, посакувајќи да покажеме совпаѓање или несовпаѓање на овие маркери помеѓу инвазивниот карцином на дојка и метастатичкиот во аксиларни јазли. Овој метод на рутински начин се изведува за секој случај со инвазивен карцином на дојка, бидејќи на пацинетите со позитивен ЕР и ПР им се нуди адјувантна хормонска терапија, обично Тамоксифен. Ки-67 е еден важен маркер на апликацијата на адјувантна терапија. (23,24,25,26)

Се предпоставува дека во повеќето случаи примарниот тумор на дојка го има истиот хормонален профил со метастазите во аксиларните јазли. Во последниве години, има некои автори кои претставија своите резултати сто покажуват за несовпаѓање во хормоналните рецептори помеѓу примарниот карцином и нивните аксиларни метастази. Во студијата на Amir E et al., е рапортиран совпаѓање на ЕР и ПР рецепторите, помеѓу примарниот тумор и метастазите во аксиларни јазли во само 46%.(27) Во ретроспективната студија на авторот Broom RJ et al., каде што беа вклучени 80 случаи, имаше несовпаѓање од 21% за ЕР и 37% за ПР.(28) Исто така во една друга ретроспективна стидија степенот на несовпаѓање беше 30% за ЕР, додека за ПР беше 39%.(29)

Податоците од нашата студија покажуваат за несовпаѓање на ЕР и ПР рецепторите помеѓу примарниот карцином и на матастатичкиот со вредност од 33.3% односно 26.7%. Оваа студија иако што вклучува мал број примероци, покажа релативно низок процент на совпаѓање во статусот на ЕР и ПР помеѓу примарниот и матастатичкиот карцином, слично со горенаведените студии, иако што во статистички аспект не покажа сигнификантна разлики во присуство на ЕР и ПР рецептори.

Во нашата студија степенот на совпаѓање на ЕР (66.7%) и ПР (73.3) статусот помеѓу примарниот тумор и метастазите во аксиларни јазли, не е во иста линија со студиите кои покажаа највисок степен за несовпаѓање. (3,30,31)

Сто се однесува за експресијата на Ки-67, податоците од нашата студија не најдоа значајна разлика на Ки-67, помеѓу примарниот тумор(80%) и кај метастази во аксиларни лимфни јазли(76.7%), односно степенот на совпаѓање беше 83.3%. Слични податоци се наоѓаат во студијата на Taefik et al.,(32), но некои други автори најдоа највисока експресија на Ки-67 во метастазите во аксиларни јазли во споредба со примарниот карцином на дојка.(33,34,35)

ЗАКЛУЧОК

Ние дојдовме до заклучок дека во нашата студија нема значајна разлика за ЕР,ПР и Ки-67 рецепторите, помеѓу примарниот тумор и метастазите во аксиларни лимфни јазли, меѓутоа во оваа студија се забележува дека степенот на совпаѓање за ЕР и ПР во овие две локации за рак на дојка не е премногу висока, и недостаток на сигнификанца во овој аспект би межел да биде поради малиот број на примероци. Поради оваа причина, се препорачува да се зголеми бројот на примероци, со цел за да можеме да достигаме до верливите заклучоци. Ова високо присуство на несовпаѓање (иако несигнификантно во моментов) на ЕР и ПР рецептори помеѓу примарниот тумор на дојка и во аксиларните метастази, не дозволува можност да се сугерира дека експресијата на една локација за ЕР и ПР да важи подеднакво и на другата локација.

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Original scientific paper

AGE-RELATED CHANGE IN GLYCEMIC CONTROL IN DIABETIC PATIENTS WITH AND WITHOUT REGULAR STRUCTURED VISITS

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ABSTRACT

Introduction The aim of this study was to evaluate glycemic control in different age groups of diabetic patients at first and last regular structured visit and to compare the results between groups with regular and irregular visits.

Materials and methods This research is a prospective, longitudinal clinical study performed in 2016-2017 involving twenty specialists in family medicine in North Macedonia. Data from 276 patients were obtained, after one year follow up, during which they were asked to have regular structured visits every 3 months. According to regularity of visits, they were divided in two groups: a) regular and b) irregular. The patients were divided in three age categories with age-adjusted target HbA1c level for optimal glycemic control: a) group I (<65 years) < 7%; b) group II (65-75 years) < 7,5%; and c) group III (>75 years) < 8%.

Results In age group <65 years with regular visits mean HbA1c was significantly improved from first to last visit (p=0,001) and significantly more patients achieved age-adjusted HbA1c target for optimal glycemic control at last visit vs. first visit (p=0,0176). This was not found in the same age group with irregular visits, as well as in the other age groups, irrespective of regularity of performed visits.

Conclusion Younger patients <65 years demonstrated significant improvement in glycemic control after performing regular structured visits. No significant improvement was seen in other age groups.

Keywords: age, HbA1c, glycemic control, diabetes, regular visits

INTRODUCTION

Diabetes management is a very complex process that requires a lot of efforts for achieving many targets (glycemia, blood pressure, lipids, weight etc.) in order to be successful. Despite the recent recommendations for avoiding glucocentricity when managing diabetes, one should not interpret these as achieving optimal glycemic control is becoming less important. On the contrary, this means that glycemic targets should be achieved, but not at a cause of compromising patient's safety. Findings from three landmark diabetes studies conducted on middle-aged and older patients with type 2 diabetes, Action to Control Cardiovascular Risk in Diabetes (ACCORD),[1] Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),[2] and the Veteran Affairs Diabetes Trial (VADT),[3] demonstrated that intensive glucose control (<6% or <6,5%) did not resulted in improved cardiovascular outcomes. ACCORD trial results demonstrated significantly higher cardiovascular

disease related mortality in the group with intensive glycemic control, as well as 3-fold increase in severe hypoglycemic events. Many studies confirmed that due to age-related decrease in ε-adrenergic receptor function elderly patients are highly susceptible to hypoglycemia and consequent increased risk to develop cognitive impairment, dementia, all-cause hospitalization, and all-cause mortality [4-7]. On the other hand, other study based on the large NHANES survey concluded that HbA1c >8.0% was associated with increased risk of all-cause and cause-specific mortality in older adults with diabetes [8]. Therefore, current treatment guidelines recommend individualized glycemic targets for diabetic patients [9-11]. Although the target for optimal glycemic control is generally set to <7%, guidelines acknowledge that tighter glycemic target of HbA1c < 7.0% [48 mmol/mol] may not be appropriate for some patients. Less stringent HbA1c goals such as <7,5% [58 mmol/mol] and <8% [64 mmol/mol] are considered appropriate for majority of elderly patients, depending on present age and life expectancy, diabetes duration, risk of hypoglycemia, established comorbidities, macrovascular and/or microvascular complications, cognitive impairment and functional dependence [11-14]. The goal can be set even higher, up to 8,5% [69 mmol/mol] if the patient is highly functionally dependant, like for example in cases of frail or dementia [11],[14].

There are many factors contributing to achieving optimal glycemic control. Although older age is associated with higher HbA1c values in general population, it can't be concluded that older diabetic patients are less likely to achieve optimal glycemic control. Some studies reported that younger age in diabetic patients is associated with worse glycemic control. [15-17]. This is also dependant on individual lifestyle interventions and treatment adherence, as well as regular diabetes monitoring. As for all chronic diseases, compliance to doctor's advices and regular visits to doctor's office is consider beneficial for diabetes management. Clinical practice guidelines recommend regular examinations at a defined time period for evaluation of diabetes management progress and introducing adequate measures timely.

The aim of this study was to compare mean HbA1c values and proportion of patients achieving age-adjusted HbA1c target for optimal glycemic control in different age groups of diabetic patients at first and last regular structured visitε, after a follow up of one year, and to compare the results between groups of patients with regular and irregular visits.

The study was approved by Ethic Committee at the Medical Faculty, "Ss. Cyril and Methodius" University in Skopje. To the best of our knowledge such study hasn't been conducted so far in North Macedonia and we believe it can bring some additional insights for better diabetes management in our country.

MATERIALS AND METHODS

This research is part of a prospective, cohort, longitudinal clinical study performed in the period 2016-2017 involving twenty specialists in family medicine from different regions in Republic of North Macedonia (Skopje, East and West). More than 400 patients with diagnosed diabetes have been recruited and followed up for one year, during which they were asked to have regular structured visits every 3 months. Inclusion criteria for selection were: patients with diagnosed type 2 and type 1 diabetes for at least one year, age >18 years, signed informed consent. Exclusion criteria were: age <18 years, diabetes in pregnancy and during breastfeeding, gestational diabetes and patients refusing therapy. At the end of the study period complete data from 276 patients were obtained. According to regularity of the visits performed, the patients were divided in two groups: a) group with regular visits - 168 (60,9%) and b) group with irregular visits - 108 (39,1%). Patients who omitted two consecutive visits were considered irregular.

The subjects were divided in three age categories: a) group I < 65 years; b) group II – 65 to75 years; and c) group III > 75 years. For each of the three groups the target level of HbA1c for optimal glycemic control was adjusted for age, as follows: a) group I < 7%; b) group II- < 7,5%; and c) group III < 8%. The targets were set based on present patient's age and life expectancy, as per current guidelines recommendations [11-14].

STATISTICAL ANALYSIS

Data was statistically analysed in SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). Qualitative series were processed by determining the coefficient of relations, proportions, and rates, and were shown as absolute and relative numbers. Quantitative series were analysed with measures of central tendency (average, median), as well as with dispersion measures (standard deviation, standard error). Chi square test was used to determine the association between certain characteristics in the groups of subjects. To test the

difference between independent/ dependent groups Kruskal-Wallis H, Wilcoxon signed rank test and McNemar Chi-squar test were used appropriately. A two-sided analysis with a significance level of p<0,05 was used to determine the statistical significance.

RESULTS

Results from this study are presented and compared between the groups of patients with REGULAR and IRREGULAR structured visits.

In the group with REGULAR structured visits (N=168), mean age was 60,5±9,6 years, median (IQR)=61,5 (56-68), minimum/maximum age 32/85 years. In the group with IRREGULAR structured visits (N=108), mean age was 58,9±10,5 years, median (IQR)=60 (53-66), minimum/ maximum age 26/80 years. For p>0,05, there was no significant difference between the groups related to age (Mann-Whitney U Test: Z=1,5606; p=0,1186).

Mean HbA1c value, as well as proportions of patient achieving age-adjusted HbA1c target for optimal glycemic control were analysed from the first vs. last visit data in the groups with regular/ irregular structured visits.

I. In the group with REGULAR structured visits we found that the highest mean HbA1c at first visit was observed in the age group < 65 years (7,6±1,7%;median (IQR)=7,4 (6,3-8,1); min/max 5,3/14,7%) vs. highest mean HbA1c at last visit in the age group 65 to 75 years (7,1±1,2%; median (IQR)=7 (6,1-7,8); min/max 5,7/12,7%). Lowest mean HbA1c at first visit was seen in the age group >75 years (6,9±1,3%; median (IQR)=6,5 (6,0-7,2), min/max 5,8/9,1%) vs. lowest mean HbA1c at last visit in the same age group (7,1±1,2%; median (IQR)=6,6 (6,4-7,3); min/max 5,9/10%). Mean HbA1c in the age group 65 to 75 years at first visit was 7,2±1,4%; median (IQR)=7,1 (6,1-7,6); min/max 5,3/12%. Mean HbA1c in the age group < 65 years at last visit was 7,1±1,1%, median (IQR)=6,9 (6,4-7,8), with min/max 5/10,8%.

No significant difference, for p>0,05, between the three age groups regarding mean HbA1c was shown both at first and last visit. (Kruskal-Wallis H test: Chi-square (2)=3,8324; p=0,1472 and Kruskal-Wallis H test: Chi-square (2)=1,1007; p=0,5767, respectively).

Significant change with Wilcoxon signed rank test, for p<0,025, regarding mean HbA1c at last vs. first visit was observed in the age group < 65 years (Z=3,305; p=0,001) in favour of lower HbA1c at last visit (Table 1). No significant change, for p>0,025, regarding mean HbA1c at last vs.first visit was seen in the other age groups, 65 to75 years (Z=0,009; p=0,993) and >75 years (Z=0,533; p=0,594).

Table 1. Wilcoxon signed rank test for HbA1c at last/first visit per age group- patients with REGULAR visits

Wilcoxon Signed Ranks Test	Last/ first Group < 65 years	Last/first Group -65 to75 years	Last/first Group >75 years
Z	(3,305)	(0,009)	(0,533)
Asymp. Sig. (2-tailed)	0,001*	0,993	0,594

* according to Bonferroni correction significant for <0,025

Regarding the proportion of patients with REGULAR structured visits achieving age-adjusted HbA1c value for optimal glycemic control, we found that in the group <65 years, for p<0,05, there was a significant difference between the first and last visit, in favour of last visit (McNemar Chi-square=5,63; df=1; p=0,0176). In groups 65 to75 years and >75 years, for p>0,05, no significant difference between the first and last visit was observed. (McNemar Chi-square=0,08; df=1; p=0,7728) vs. (McNemar Chi-square=0,50; df=1; p=0,4795). (Table 2)

Table 2. Analysis of achieving age-adjusted optimal glycemic control (HbA1c) per age group at first/last visit for group with REGULAR structured visits

REGULAR STRUCTURED VISITS						
Age groups			HbA1c1 last visit			p
			yes	no	total	
Group < 65 years						
HbA1c1 first visit	yes	N	34	8	42	McNemar Chi-square=5,63; df=1; p=0,0176*
		%	31,5%	7,4%	38,9%	
	no	N	22	44	66	
		%	20,4%	40,7%	61,1%	
	total	N	56	52	108	
		%	51,9%	48,1%	100%	
Group - 65 to75 years						
HbA1c1 first visit	yes	N	29	6	35	McNemar Chi-square=0,08; df=1; p=0,7728
		%	56,9%	11,8%	68,6%	
	no	N	6	10	16	
		%	11,8%	19,6%	31,4%	
	total	N	35	16	51	
		%	68,6%	31,4%	100%	
Group > 75 years						
HbA1c1 first visit	yes	N	6	1	7	McNemar Chi-square=0,50; df=1; p=0,4795
		%	66,7%	11,1%	77,8%	
	no	N	1	1	2	
		%	11,1%	11,1%	22,2%	
	total	N	7	2	9	
		%	77,8%	22,2%	100%	

1age-adjusted target for optimal glycemic control

II. In the group with IRREGULAR structured visits the highest mean HbA1c at first vist was seen in age group < 65 years (7,5±1,5%; median (IQR)=7,3 (6,5-8,3); min/max 5/14,6%) vs. highest mean HbA1c at last visit in age group >75 years (7,5±0,8%; median (IQR)=7,8 (7,1-8,1); min/max 6,4/8,3%). Lowest mean HbA1c at first vist was seen in age group >75 years (7,2±0,8%; median (IQR)=7 (6,9-7,8); min/max 6/8,2%) vs. lowest mean HbA1c at last vist in age group 65 to 75 years (7,2±1,7%; median (IQR)=7 (6,2-7,6); min/max 4,6/12%). Mean HbA1c in the age group 65 до75 years at first visit was 7,4±2%; median (IQR)=7,1 (6,0-7,7); min/max 4,9/12,4%. Mean HbA1c in the age group < 65 years at last visit was 7,3±1,8%; median (IQR)=7 (6,2-8,0); min/max 4,2/17,4%.

For p>0,05, no significant difference between the three age groups was seen regarding mean HbA1c at first and last visit (Kruskal-Wallis H test: Chi-square (2) =1,1007; p=0,5767 and Kruskal-Wallis H test: Chi-square (2) = 1,2443; p=0,5368, respectively).

For p>0,025, no significant differences regarding mean HbA1c at last vs. first visit was observed in each of the three age groups; (Table 3)

* significant for p<0,05

Table 3. Wilcoxon signed rank test for HbA1c at last/first visit per age group- patients with IRREGULAR visits

Wilcoxon Signed Ranks Test	Last/ first Group < 65 years	Last/first Group -65 to75 years	Last/first Group >75 years
Z	(1,300)	(0,114)	(2,023)
Asymp. Sig. (2-tailed)	0,194	0,909	0,043

* according to Bonferroni correction significant for <0,025

Regarding the proportion of patients with IRREGULAR structured visits achieving age-adjusted HbA1c value for optimal glycemic control, for p>0,05, the results demonstrated no significant difference, between first and last visit in all three groups (Table 4)

Table 4. Analysis of achieving age-adjusted optimal glycemic control (HbA1c) per age group at first/last visit for group with IRREGULAR structured visits

IRREGULAR STRUCTURED VISITS						
Age groups			HbA1c1 last visit			p
			yes	no	total	
Group < 65 years						
HbA1c1 first visit	yes	N	21	6	27	McNemar Chi-square=2,45; df=1; p=0,1175
		%	28,4%	8,1%	36,5%	
	no	N	14	33	47	
		%	18,9%	44,6%	63,5%	
	total	N	35	39	74	
		%	47,3%	52,7%	100%	
Group - 65 to75 years						
HbA1c1 first visit	yes	N	16	3	19	McNemar Chi-square=0,08; df=1; p=1,0000
		%	55,2%	10,3%	65,5%	
	no	N	4	6	10	
		%	13,8%	20,7%	34,5%	
	total	N	20	9	29	
		%	69%	31%	100%	
Group > 75 years						
HbA1c1 first visit	yes	N	3	1	4	McNemar Chi-square=0,00; df=1; p=1,0000
		%	60%	20%	80%	
	no	N	0	1	1	
		%	0%	20%	20%	
	total	N	3	2	5	
		%	60%	40%	100%	

1age-adjusted target for optimal glycemic control * significant for p<0,05

DISCUSSION

According to the results from our study younger patients (age group <65 years) regularly visiting doctors and performing necessary examinations as per clinical guidelines recommendations demonstrated significant improvement in glycemic control, after a follow up period of one year. Significantly lower mean HbA1c values (p=0,001) were found at last vs. first visit and significantly more patients in this group achieved age-adjusted HbA1c target for optimal glycemic control at last visit vs. first visit (p=0,0176). This was not observed in the same age group with irregular visits. No significant improvement in glycemic control was observed in the other age groups, irrespective of regularity of performed visits. However, it is fair to mention that the age group <65 years had the highest mean HbA1c value at first visit both in patients with regular structured visits (7,6±1,7%) and in those with irregular structured visits (7,5±1,5%). This finding correlates with findings from other studies demonstrating that younger diabetic patients have poorer glycemic control. [15-19]. This is becoming even more important having in mind that the age-adjusted target for younger patients should generally be lower compared to older patients targets, unless there are serious concomitant conditions and complications limiting life expectancy or posing a risk for severe hypoglycemia. But, despite the fact the younger age can be associated with worse glycemic control, this was also found for irregularity of visits. [19]. Our findings in the age group <65 years leads to a conclusion that regular structured visits contributed to improvement in glycemic control in this age group, whereas irregular did not. Regular structured visits per se should mean more vigilant diabetes monitoring and consequent interventions, like changes in lifestyle behavior and treatment modalities, when necessary. Lifestyle behavior was found to be strongly associated with HbA1c levels in middle aged (51-64 y) patients with type 2 diabetes. [20]. This could also be one of the reasons why regular visits in our study resulted in significant improvement in glycemic control in this age group, but in order to confirm this further analysis on lifestyle changes should be performed. In our study we also found that older age group > 75 years, although the result was insignificant, was the only group demonstrating

worsening in glycemic control after a follow up of one year, in both groups with regular and irregular visits. A systematic review evaluated longitudinal trends in HbA1c and associated factors in diabetic patients and concluded that younger age was associated with poorer HbA1c trajectories in type 2 diabetes. [21]. In our study, we saw different results, even though HbA1c trends in all age groups seems to be stable, as per criteria used in this systematic review (change in HbA1c during follow up from baseline of less than 1%). Another longitudinal study evaluated predictors of glycemic control in type 2 diabetes [22]. In this study authors acknowledge that mean HbA1c fluctuated differently over time for various age groups. The youngest age group <50 years initially declined in HbA1c after three months and then steadily rose in the following fifteen months, whereas other age groups 50-65 years and >65 years fluctuated over time. It is believed that younger patients, with shorter diabetes duration, and especially if below one year from diagnosis are willing to introduce lifestyle changes at the beginning, but the motivation seems to decline over time. Our study did not include patient with less than one year from diagnosis, so we believe that improvement in glycemic control in our age group <65 years is not due to "initial motivation", but rather regularity of visits performed maybe contributes to "reintroduced motivation" in this age group.

Study limitations

Age-adjusted glycemic targets used in our study are just a small step forward towards individualized glycemic targets and are intended to give us as realistic picture as possible. However, these targets did not take into consideration important factors such as diabetes duration, risk of hypoglycemia, presence of complications and comorbidities, as well as patient's preference. Therefore, one should not simply translate those targets into clinical practice without considering other factors.

In our study, multivariate adjustment for other variables than age has not been performed when evaluating HbA1c change from baseline to last visit.

CONCLUSION

Understanding factors contributing to better glycemic control is of utmost importance for successful diabetes management. Our study demonstrated that regular structured visits in diabetic patients can contribute to improving glycemic control in selected age group of patients <65 years, but not in other age groups. Further analysis for evaluating other contributing factors would be beneficial.

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Profesional paper

ЗАСТАПЕНОСТ НА ВЕНТРАЛНАТА ХЕРНИА ВО ОПШТИНА ГОСТИВАР ВО ПЕРИОД ОД 2014-2018 ГОДИНА

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АБСТРАКТ

Вентрална херниа (инцизиона херниа) претставува протрузија на цревата и/или другите ткива на абдоменот низ лузната од претходната абдоминална операција, затоа уште се означува и како постоперативна херниа. Целта на овој труд е покажување на застапеноста на вентралната херниа во општина Гостивар во период од 2014-2018 година. Студијата е извршена проспективно во период од 2014-2018 година во хируршкото одделение во општа болница "Ферид Мурад„- Гостивар. Обработени се 92 пациенти, од кои 31 се мажи, додека 61 се жени. Користени оперативни методи за оперативен тратман на вентралната херниа се отворена метода со директна сутутра и отворена метода со поставување на мрежичка. Од 92 пациенти дијагностицирани со вентрална херниа 33,69% се од машки пол (31 пациенти) , додека 66,31% се од женскиот пол (61 пациенти). Од вкупно 92 пациенти, 87 (94,56%) пациенти се оперирани со отворена метода со директна сутура, додека 5 (5,44%) пациенти се оперирани со отворена метода со поставување на мрежичка.

Клучни зборови: вентрална херниа, инцизиона херниа, постоперативна кила

ВОВЕД

Вентрална херниа (инцизиона херниа) претставува протрузија на цревата и/или другите ткива на абдоменот низ лузната од претходната абдоминална операција, затоа уште се означува и како постоперативна херниа. Предиспонирачки фактори за настанувањето на вентралната херниа се: 1. Местото на оперативниот рез; рана во фаза на зараснување локализирана во средната линија на абдоменот претставува најслабото место за настанување на инцизионите хернии, 2.Фактори кои влијаат врз зараснувaето на раната; инфекција, хематом, груба оперативна техника со трауматизирање на ткивата и неисправно приближување на слоевите на раната, постоперативно кашлање,3.Оштетување на моторни нерви при оперативен зафат.(1,2) Инциденцата на вентралната херниа е 10%, после првиот рецидив е 50%, после другиот рецидив е 55%, додека после секој следен рецидив е околу 75%(3). Оперативниот третман на вентралната кила може да биде со отворена метода или лапароскопска метода. Отворената метода-пластика на предниот абдоминален sид може да биде доста сериозна интервенција а во постоперативниот ток може да се појави повторно рецидив. на истата Во креирањето на пластиката на предниот абдоминален sид може да се направи директна – сутура на анатомските слоеви на абдоминалниот sид и санирање на дефектот или, доколку постои поголем дефект или изразена слабост на абдоминалниот sид, да се користат разни видови на мрежи кои во зависност

од типот, може да се пласираат интраперитонеално или екстраперитонеално. За разлика од отворениот оперативен пристап, лапараскопскиот третман на вентрална кила е понова метода. Операцијата се изведува со помош на посебни инструменти кои се воведуваат во абдоминалната празнина преку водичи – троакари- пласирани на строго определени места на предниот абдоминалниот ѕид. Типот на оперативниот пристап сепак зависи од видот на вентралната кила, големината на вентралната кила, искуството на хирургот и материјалите со кои располага хирургот(2,4,5,6).

ЦЕЛ

Целта на овој труд е покажување на застапеноста на вентралната херниа во општина Гостивар во период од 2014-2018 година.

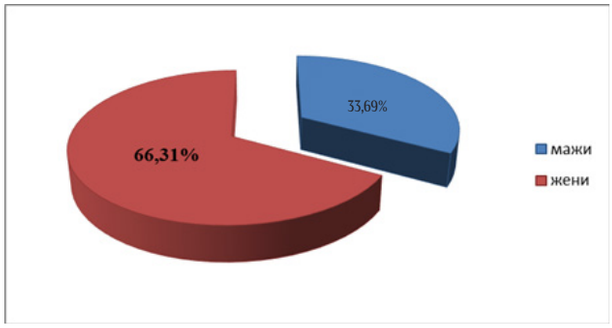
МАТЕРИЈАЛИ И МЕТОДИ

Студијата е извршена проспективно во период од 2014-2018 година во хируршкото одделение во општа болница “Ферид Мурад„- Гостивар. Обработени се 92 пациенти, од кои 31 се мажи, додека 61 се жени.

Користени оперативни методи за оперативен тратман на вентралната херниа се отворена метода со директна сутутра и отворена метода со поставување на мрежичка.

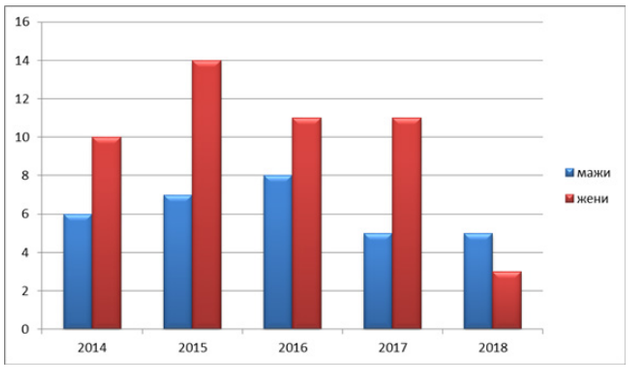
РЕЗУЛТАТИ

Од 92 пациенти дијагностицирани со вентрална херниа 33,69% се од машки пол (31 пациенти) , додека 66,31% се од женскиот пол (61 пациенти).



Графикон 1. Застапеност на вентрална херниа според пол

Од вкупно 92 пациенти, во 2014 година се оперирани 16 пациенти (17,39%), од кои 6 се мажи, додека 10 се жени. Во 2015 година се оперирани 21 пациенти (22,83%), од кои 7 се од машкиот пол и 14 пациенти од женскиот пол. Во 2016 година се оперирани 19 пациенти (20,65%), од кои 8 се од машкиот пол, додека 11 се од женскиот пол. Во 2017 година се оперирани 16 пациенти (17,39%), од кои 5 се од машкиот пол, додека 11 пациенти се од женскиот пол. Во 2018 година се оперирани 20 пациенти (21,74%), од кои 5 се од машкиот пол, додека 15 се од женскиот пол.



Графикон 2. Застапеност на вентралната херниа според полот во соодветните години во период од 2014-2018 година.

	2014		2015		2016		2017		2018		
возраст	м	ж	м	ж	м	ж	м	ж	м	ж	вкупно
10-19	/	/	/	/	1	/	/	/	/	/	1
20-29	1	/	1	1	/	/	1	/	/	/	4
30-39	/	1	/	1	/	1	/	1	2	1	7
40-49	1	1	1	3	2	1	/	1	1	1	12
50-59	2	3	3	4	3	5	1	4	/	6	31
60-69	1	3	1	3	/	3	1	2	2	6	22
70-79	1	2	1	2	2	1	2	3	/	1	15
вкупно	6	10	7	14	8	11	5	11	5	15	92

Табела 1. Застапеност на вентралната херниа по пол и возраст во период од 2014-2018 година.

Од вкупно 92 пациенти, 87 (94,56%) пациенти се оперирани со отворена метода со директна сутура, додека 5 (5,44%) пациенти се оперирани со отворена метода со поставување на мрежичка.

ДИСКУСИЈА

Вентралните кили настануваат најчесто на местото на оперативните резови. Причини за појава на вентрална кила се груба хируршка работа, појава на постоперативна инфекција на оперативната рана, користење на лоши материјали за затворање на оперативната рана, и затворање на оперативната рана под тензија, како и лошата општа состојба на пациентот хипопротеинемија и анергија кај тешки болни. Најчесто вентралните кили се појавуваат ако во постоперативниот период пациентот е изложен на поголем физички напор и појава на зголемен абодминален притисок (напад на кашлање, појава на запек и слично) како и, присуство на колостома или илеостома.- појава на парастомални кили(2,3).

Вентрална кила може да се појави после секоја хируршка интервенција каде што имаме заздравување на абдоминалниот sид дури и после минимални инцизии на абдоминалниот sид како при лапароскопските интервенции. Во некои случаеви, вентралните кили може да достигнат огромни димензии и во килната кеса да се наоѓа голем дел од цревата и во такви случаеви, доколку таа состојба е подолготрајна, реконструкцијата на абдоминалниот sид може да доведе до компресија на цревата и зголемување на абдоминалниот притисок, ретко до намалена васкуларизација на цревата и отежнато дишење кај пациентот поради подигнување на дијафрагмата(1,2).

Оперативниот третман на вентралната кила може да биде со отворена или лапароскопска метода. Отворената метода- пластика на предниот абдоминален sид може да биде доста сериозна интервенција а во постоперативниот ток може да се појави повторно рецидив. на истата Во креирањето на пластиката на предниот абдоминален sид може да се направи директна – сутура на анатомските слоеви на абдоминалниот sид и санирање на дефектот или, доколку постои поголем дефект или изразена слабост на абдоминалниот sид, да се користат разни видови на мрежи кои во зависност од типот, може да се пласираат интраперитонеално или екстраперитонеално. За разлика од отворениот оперативен пристап, лапараскопскиот третман на вентрална кила е понова метода. Операцијата се изведува со помош на посебни инструменти кои се воведуваат во абдоминалната празнина преку водичи – троакари- пласирани на строго определени места на предниот абдоминалниот sид(2,4,5,6).

Типот на оперативниот пристап сепак зависи од видот на вентралната кила, големината на вентралната кила, искуството на хирургот и материјалите со кои располага хирургот. Кај нас најчесто се применува операција на вентрална херниа со отворена метода.

Постоперативно, најчеста компликација е инфекција на оперативната рана, појава на рецидив на вентралната кила, а при третирање на големи вентрални кили, враќањето на содржината на килната кеса во абдоминалната празнина може да доведе до пореметување на васкуларизацијата на цревата и зголемување на интраабдоминалниот притисок поради што понекогаш се прават и делумни ресекции на цревата со цел да се смести содржината на килната кеса во абдоминалната празнина(3,7).

Во еден од трудовите кои беа цел на истражување, била направена студија со две групи на пациенти, од кои едните беа третирани со мрежичка а другите со модифицирана Mayo метода. И покрај поголемата стапка на пројавени компликации, се покажало дека оперативниот зафат со користење на мрежичка е посуперирорен во однос на директна сутура. Оперативните резултати се следени 28 месеци и пациентите беа поделени во две групи, односно, тие беа поделени по пол – женски и машки. На пациентите од групата со машки пол била изведена операција со користење на мрежичка, додека пак кај групата составена од женски пол била изведена традиционална операција. Она што се покажало како резултат кај ова истражување е дека резултатите се подобри кај групата со машки пол, односно, кај оваа група пациентите пократко време престојувале во болница, процентот на инфекции е намален, и она што е доста важно е дека бројот на потребни реоперации е намален кај групата со пациенти од машки пол(8).

ЗАКЛУЧОК

- Во хируршкото одделение во општа болница “Ферид Мурад„- Гостивар, во период од 2014-2018 година, вкупно 92 пациенти се дијагностицирани со вентрална кила, при што најголем број од пациентите се од женскиот пол (61 пациенти или 66,31%) во однос на машкиот пол (31 пациенти или 33,69%).
- Најголем број на пациенти (31 пациенти или 33,69%) оперирани од вентрална херниа се во возрасна група од 50-59 години.

- Од вкупно 92 пациенти, најголем број на пациенти (87 пациенти или 94,56%) се оперирани со отворена метода со директна сутура.
- Користење на адекватна метода за успешно лекување на вентрална херниа е многу битен од социјален и економски аспект.

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Profesional paper

ADIPONECTIN AND THE ROLE OF INTERLEUKIN-6 (IL-6) IN INSULIN RESISTENCY AND DIABETES MECHANISM AND THE ROLE OF TUMOR NECROSIS FACTOR (TNF- α) IN PRE-DIABETES, INSULIN RESISTENCY AND OBESITY MECHANISMS

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ABSTRACT

Introduction: Diabetes represents an important social disease, which affects almost 5-8% of world population. (Kodama et al.,2013). The most common forms of diabetes are: type I diabetes, insulin dependent, or youth type, and type II diabetes, or non-insulin dependant, also adulthood diabetes.

Aim of study: Fructose effect on carbohydrate, adiponectin, insulin and other metabolic parameters metabolism. The role of interleukin 6 (IL-6) in mechanism of insulin resistency and diabetes and the role of tumor necrosis factor (TNF- **α**) in mechanisms of obesity, insulin resistance and pre-diabetes.

Material and methods: 128 Adult rats (3 months of age), Wistar species of both genders, weighting 160-180g and 65 white young rats (10-25 days) weighting 45-60g were taken for purposes of this study. The number of experimental animals in individual groups is between 5-8 while the details are added in the results section. The application of palm oil was conducted through special probe using oral administration straight into gastro-intestinal system.

Results: Figure 1 shows the differences of TNF-**α** after palm oil administration. There are statistically significant raised levels of this cytokines in blood of both young and adult rats compared to control cases. In Figure 2 it is emphasized the effect of palm oil (30 and 60 days) in IL-6 blood levels of young and adult male rats. Figure 3 shows the impact of palm oil, applied 30 and 60 days respectively against GTT of adult rats of male gender. The results of GTT studies on young rats are shown in Figure 4. They show the differences in GTT, which are statistically significant in day 60 compared to 30 days of palm oil treatment.

Conclusion: Elongated administration 60 days of palm oil in experimental rats of adult and young rats, raise the blood levels of TNF-**α** and IL-6, thus changing metabolism of carbohydrates with data supporting pre-diabetic conditions.

Key words: adiponectin, palm oil, cytokines

Diabetes is an important social disease, affecting 5-8% of world population. The most common forms of diabetes are: type I diabetes, insulin dependent, or youth type, and type II diabetes, or non-insulin dependant, also adulthood diabetes.

The pathogenesis of diabetes is wide and many key factors are included like genetics, nourishing, infection, stress, enviroment pollutants and others, while in most cases there is a combination of two or more of those factors. The main pathogenic event is the distruption of pancreatic beta-cells function, which produce and secrete the hormone - insulin, important for carbohydrate metabolism in both human and a lot of experimental naimals. Diabetes is characterized with disruption of carbohydrate, protein and lipid metabolism and it is related with many risk complications.

Many factors leading to diabetes are not clear enough, though. We can mention here obesity, free radicals and some cytokines which may be responsible for diabetes development. Literature analysis of adiponectin role are

published by (Gateva P, Besim M, Boyadjieva N, 2012). It is documented that adiponectin is produced and secreted by adipocytes. It belongs to anti-infective adipocites and there is data that proves that during weight gaining, adiponectin production and secretion is reduced. The research results clearly show that reduced production of adiponectin is positively correlated with insulin resistency, atherosclerosis and dislipidemy (Kadowaki, 2005). Adiponectin appears from different cytokines which are active during inflammation. It is also proved that TNF-**α** and PPAR-γ reduce gene expressin for adiponectin. Studies on substances which raise the sensitivity of insulin receptors for insulin, show that adiponectin levels in both human and rats are raised. Over-weight patients, after losing weight show the tendency of raising adiponectin levels and also improve insulin resistency. (Despres et al., 2005).

Generally, all the published facts show that adiponectin produced by cytokines and adipocytes has a role on type II diabetes pathogenesis. The widely fructose use as a replacement for glucose raise the question for its effect on adiponectin. There are only few studies on farmacological substances and food combinations. Some of the studies are focused on the effect of fructose towards indicator changes of carbohydrates and adiponectin.

Adiponectin is raised during adipocyte differentiation (Carbone et al., 2012). Three isoforms of adiponectin are well known: low molecular weight, medium- and high molecular weight (Magkos et al., 2007). HMW adiponectin is the most biologicallyu active form and it establishes changes of total adiponectin during obesity (Almeda-Valdes et al., 2010). Adiponectin can also rasie the cell oxidation, thus improving insulin resistency (Carbone et al., 2012), and also can stimulate gluconeogenesis in the liver, which physiologically reflects on lowering blood glucose levels. Adiponectin also has inflammatory activity and it's role is in insulin regulation of T-Cells (Carbone et al., 2012). IL-6 is added onto mechanisms, through which obesity activates insulin resistance. Many authors establish the important role of TNF-**α** and IL-6 in activating insulin resistance. One of the hypothesis is that, during adipose tissue growth there is increased adipocyte hypoxia, which is expressed against transcriptional hypoxia inducible factor 1, with changes in NF-κB activation, ultimately leading to adipocyte function changes and TNF-**α** and IL-6 secretion (Bruning et al., 2012).

The role of tumor necrosis factor-alpha (TNF-α) in mechanism of weight gaining, insulin resistance and pre-diabetes

TNF-**α** is an anti-inflammatory cytokine, which is produced by various types of cells, but mainly from macrophages and lymphocytes. There is data that suggest that is also produced by fat cells during weight gaining and also that its secretion is also raised. The studies on TNF-**α** and weight gaining show that there is difference between persons with and without fat mass increase. Also there are studies with show the contrary, that there is no correlation between these two parameters (Codoñer-Franch P et a., 2012). This has led researches to stand behind the hypothesis that leptin, adiponectin and other important metabolic factors regulate the secretion of TNF-**α**. Most of the researches have come to the conclusion that more studies are required to present role of TNF-**α** in humans in obesity, as most of the facts so far are based on experimental studies.

As TNF-**α** is an important inflammatory cytokine, its role in obesity development is undervalued. Clinical and experimental studies suggest that TNF-**α** regulates insulin sensitivity through insulin receptors. The studies on different nourishing and farmacological substances on TNF-**α** and diabetes risk are new and provide more facts on discussion about the role of cytokines in insulin sensitivity mechanism.

The role of interleukin 6 (IL-6) in insulin resistance and diabetes mechanism

As we have already state, IL-6 is produced and secreted by fat tissue. Curat et al (2004) studies show that adipocytes secrete IL-6 and that it does take part on glucose and lipid homeostasis regulation. Chung et al (2006) studies document decrease of GLUT4 transporters. There are studies that suggest that para-adipocytes secrete considerably more IL-6 than adipocytes (Mack et al., 2009). Also, we can agree that pro inflammatory cytokines take part on diabetes pathogenesis (Calle MC et al., 2012). Studies (Bahceci M et al., 2007) on healthy persons with/without obesity and on diabetic patients with/without obesity has shown different raised levels of IL-6 mainly on obesse ones. It is important the correlation between IL-6 raised levels and raised C-reactive protein on obesse people with or without diabetes. The highest values are shown where both factors are present, obesity and diabetes. Also data suggests that IL-6 stimulates insulin secretion through increased GLP-1 expression on pancreatic cells (Ellingsgaard et al., 2011).

Raised levels of IL-6 are linked with damaged function of the liver, and carbohydrate disturbance. Analysis show that increased production and secretion of IL-6 in obesity leads to increased production of insulin and thus leading to decrease of pancreatic beta cells function decrease. Provided all the published materials, it can be concluded that IL-6 produced by WAT, skeletal muscle and liver, has a role on mechanisms of insulin sensitivity and type 2 diabetes development.

Aim of study

Fructose effect on carbohydrate, adiponectin, insulin and other metabolic parameters metabolism. Interleukin 6 role on diabetes and insulin resistance mechanism. The role of TNF-ε in obesity, insulin resistance and pre-diabetes mechanisms.

Materials and methods

128 Adult rats (3 months of age), Wistar species of both genders, weighting 160-180g and 65 white young rats (10-25 days) weighting 45-60g were taken for purposes of this study. The number of experimental animals in individual groups is between 5-8 while the details are added in the results section.

Standard conditions of specific rooms and temperature were met as was needed for experimental animals care. For the control group it was provided palm oil while for experimental group pig oil was used. All of the rats had water acces of Ad Libitum type. During fructose studies rats had access on fructose solution, which is described better on result section.

Results

Results are shown in Figures below. Figure 1. shows TNF-ε changes under palm oil influences. Raised levels of these cytokines in adult rats blood compared to control group are statistically significant. (*p<0.05; **p<0.001).

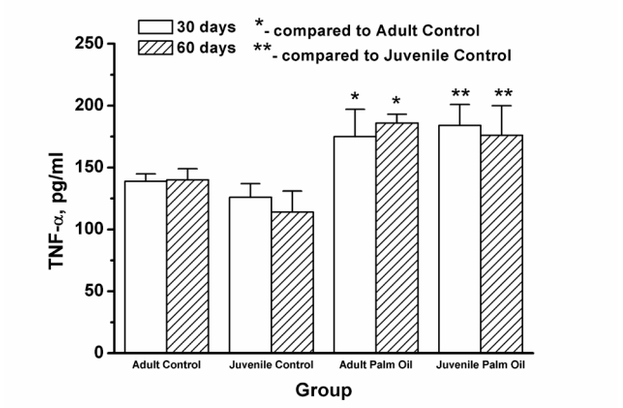

Figure 1. TNF-**α** levels in adult and young Wistar line rats serum with or without application of palm oil during 30 and 60 days.

Statistical analysis

One way ANOVA: P<0.0001: the variances among column means are significantly greater than expected by chance.

Bartlett: The SD's belong to the same population.

Bonferoni: tcr=2.697; H0: if t>tcr, then P<0.05

Discussion

In each group of rats palm oil application bring to statistically significant raised levels of TNF-**α** in blood serum (p<0.001 for young rats, p<0.01 for adult ones). The power of this effect is not influenced neither from age nor from timing of palm oil application. Results of raised levels of TNF **α** under the influence of palm oil application show statistically significant results both on adult rats and young rats compared to control groups. It is well known that TNF **α** is a pro-inflammatory cytokine, and for the first time the results show that its levels raise after continued application of palm oil in experimental animals of different ages. Results show that there is an increased risk either on young or adults under palm oil influence.

We have continued studies on defining second cytokine IL-6. In figure 2 are shown changes of IL-6 levels under palm oil application. Reports show significant changes at young rats compared to adult rats, and also both groups show statistically significant between experimental group and control group.

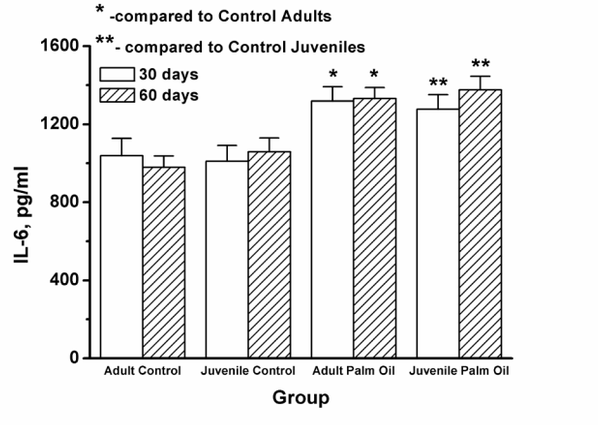

Figure 2. Palm oil effect (30 and 60 days) on blood IL-6 levels on juvenile and adult male rats.

Data statistical analysis

One way ANOVA: P<0.0004. Variations among column means significantly differ than expected by chance; Bartlett: SD'd belong to the same population; Bonferony: critical t=3.418.

Discussion

1. Palm oil application causes statistically significant raised levels of IL-6 in both groups.
2. In same conditions, IL-6 levels are not influenced by continuation of studies, so it is reckoned that increased levels will be the same in day 30 and 60 respectively

During studying time it was realised GTT in day 30 and 60 respectively. In Figure 3 are presented results from GTT. These results show the changed levels which are more important in minute 90 and speak same as data for prediabetes.

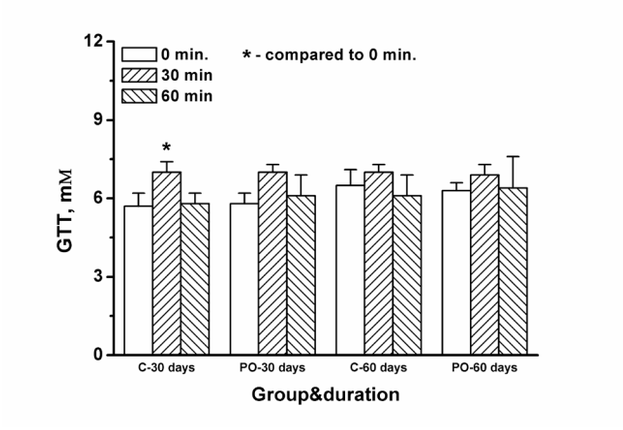

Figure 3. Palm oil effect, applied on day 30 and 60, on GTT levels of adult male rats

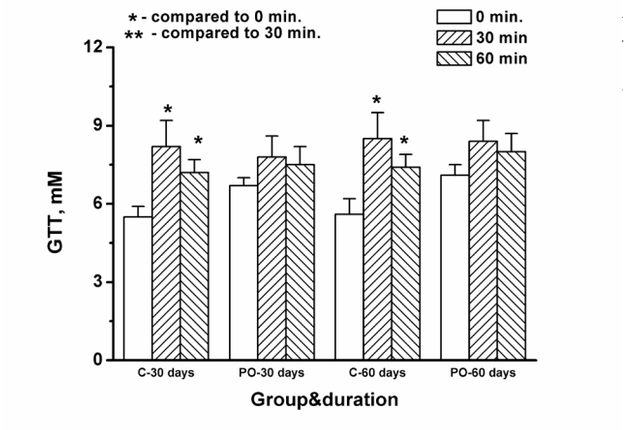

Figure 4. Palm oil effect on young male rats GTT applied on day 30 and day 60.

Discussion

Generally speaking, results show development of prediabetes with a significant risk at young rats chronically treated with palm oil. Raised levels of both cytokines are shown. Pre-diabetes condition correlates with raised levels of TNF-**α** and IL-6, and to see these changes in this study we have demonstrated those blood levels on male experimental rats, under palm oil effect. It is known that this cytokine takes part in inflammation mechanism (Michaud et al., 2013; Zhang et al., 2013). Studies have shown data in which inflammation has a role on diabetes pathogenesis (Everard et al., 2013; Di marco et al., 2013; Pedicino et al., 2013; Game et al., 2013; Donathy, 2013; Cildir et al., 2013 . Furthermore, published data support that obesity is linked with risk of inflammation (Ramsay et al., 2013; Sobieska et al., 2013; Carillon et al., 2013; Grant et al., 2013; Borgesson et al., 2013; Wright et al., 2013).

Experimental studies and their result show that palm oil in blood raise levels of pro inflammatory cytokines. This can aid as a prove that prediabetes development in experimental animals happens because of TNF -**α** and IL-6. Differences, which has been documented between young and adult rats, prove to be a high risk for diabetes development after continuous usage of palm oil from youth and adolescents. This data are of the first published, but are a basis for future studies on mechanism through which palm oil changes both cytokines and carbohydrate metabolism.

Conclusion

60 days elongated administration of palm oil, in experimental rats of adult and young age, raise blood levels of TNF-**α** and IL-6 changes metabolism of carbohydrates with data also supporting the development of pre-diabetic condition. More important, is the risk which appears in young, non mature experimental rats. If we make a correlation with humans we can conclude that individuals who use food products which contain palm oil, will be more predisposed to develop health disturbances which can cause pre-diabetic condition and later leading to diabetes.

Recommendation

From the results in our scientific research we can recommend: to take care in usage of food products which contain palm oil, specially from everyday usage of these foods. This represents a good health education for adolescents and youth individuals.

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Profesional paper

СТАПКА НА РЕЦИДИВНИ КРВАВЕЊА ПО АРГОН ПЛАЗМА КОАГУЛАЦИЈА И ИНЈЕКЦИСКА ТЕРАПИЈА СО АДРЕНАЛИН И ПОЛИДОКАНОЛ КАЈ КРВАВЕЧКИ АНГИОДИСПЛАЗИИ ВО ГОРНИТЕ ПАРТИИ НА ГАСТРОИНТЕСТИНАЛНИОТ ТРАКТ

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ВОВЕД

Ангиодисплазиите на желудникот и дуоденумот се причина за горно гастринтестинално крвавење и кај 4% -7% од лицата со ангиодисплазии. Тераписките методи што се користат за нивното лекување се ендоскопски, а во нив спаѓаат: аргон плазма коагулација (АПК), техники на електрокоагулација, механичка хемостаза со клипсирање, ласерска фото-коагулација и инјекциска терапија со склерозантни средства.

Цели: Да се утврди стапката на рецидивни крвавења кај пациенти со крвавечки ангиодисплазии во горните партии на ГИТ третирани со АПК и инјекциската терапија со раствор на адреналин и полидоканол.

Материјал и методи: Во студијата се вклучени 35 пациенти третирани со АПК, и 15 пациенти со инјекциска терапија со раствор на адреналин и 1,5% р-р на полидоканол, аплицирани во и околу самата ангиодисплазија. Двете тераписки опции се реализирани со ендоскопски пристап. Пациентите се следени во тек на 4 визити, а на втората и третата визита се направи ендоскопска контрола.

Резултати: Испитани се вкупно 50 пациенти на возраст од 18 до 64 години (средна возраст 55 години). Од нив 32 (64%) машки пациенти и 18 (36%) женски пациенти лекувани во тек 2 години со средна возраст од 55 години. Анализата покажа повисока стапка на рецидивни крварења кај пациентите третирани со адреналин, при што .се утврди статистички значајна разлика Стапката на рецидивни крварења беше сигнификантно повисока кај пациентите кои беа третирани со адреналин - $p<0,01$. Потреба од трансфузија на миени еритрицити имаа 34 пациенти (68%) во тек на првата хоспитализација.

Заклучок: Ендоскопијата е клучна процедура во дијагностицирање и лекувањето на ангиодисплазиите во гастроинтестиналниот тракт. Третманот на ангиодисплазиите на горните партии на ГИТ со АПК е сигурна метода со ниска стапка на несакани ефекти и висок степен на тераписка ефикасност. Оваа студија потврдува пониска стапка на рецидивни крвавења, а со тоа, повисока тераписка ефикасност кај пациентите третирани со АПК.

Клучни зборови: рецидивни крвавења, ангиодисплазија, аргон плазма коагулација.

Вовед : Ангиодисплазиите (АД) се аберантни крвни садови кои може да имаат различна локализација, но најчесто се наоѓаат во гастроинтестиналниот тракт. Иако анатомски се слични на телангектазите, сепак се разликуваат од нив. Истотака се сретнуваат во склоп на системски и конгенитални болести. Таксономијата главно се базира на ендоскопскиот изглед (1).

АД е најчеста васкуларна малформација на ГИ тракт и најчесто се открива кај постари пациенти. Почесто се лоцираат во цекум и на асцендентен колон.. Клиничката презентација може да варира од асимптоматска и некрваречка до живото загрозувачка хеморагија (2).

Преваленција на ангиодисплазиите тешко може да се процени. Според некои автори, таа изнесува околу 0,8% (3), иако, со примена на доволно сензитивни дијагностички методи, преваленцата е веројатно далеку повисока од онаа што се констатира во клиничката пракса (4). Се смета дека 40-60% пациенти имаат повеќе од една ангиодисплазија

(5). Класификацијата на ангиодисплазиите се базира на локализацијата, големината и според бројноста на ангиодисплазиите (табела број 1).

Според локализација	Според величина	Според бројност
Гастрични	Мали (со пречник < 2 мм)	Солитарни (n=1)
Дуоденални	Интермедијарни (пречник од 2 до 5 мм)	Мултипли (n=2 до 10)
Јејунални		
Илеални	Големи (пречник >5 мм)	Дифузни (n>10)
Колонски		

Табела број 1. Класификација на ангиодисплазии (6)

European Endoscopy Club in: Schmit A, van Gossum A. Proposal for an endoscopic classification of digestive angiodysplasias for therapeutic trials. Gastrointest Endosc 1998; 48:659.

Ангиодисплазии на горни гастроинтестинални партии.

Ангиодисплазиите на желудникот и дуоденумот се причина за горно гастринтестинално крвавење и губиток на крв кај 4-7% од лицата со ангиодисплазии (7). Манифестното и окултното крварење се присутни кај 49% од пациентите кои имаат АД, а кај останатите 51% се сметаат за случаен наод (8).

Потреба од терапија на АД

Кај сите пациенти со окултно крвавење и манифестна сидеропенична анемија се советува третман во тек на ендоскопскиот преглед, дури и кога нема знаци за активно крвавење. Доколку е потребно, кај пациентите дополнително треба да се препорача терапија со препарат на железо (9).

Тераписките методи

Во лекувањето на ангиодисплазиите може да се користат следниве модалитети: ендоскопски, рендгенолошки, хируршки и медикаменотзни опции.

Ендоскопскиот третман вклучува: аргон плазма коагулација (АПК), техники на електрокоагулација, механичка хемостаза со клипсирање, ласер фото коагулација и инјекциска терапија со склерозантни средства (10). Покрај нив, може да да се користат и ангиографија со емболизација (11).

Аргон плазма коагулација (АПК).

Аргонската плазма коагулација или АПЦ е медицинска ендоскопска постапка која се користи првенствено за контрола на крварење од одредени лезии во гастроинтестиналниот тракт. Се администрира за време на езофагогастродуоденоскопија или колоноскопија.

АПК вклучува употреба на млаз од јонизиран гас на аргон (плазма) кој е насочен преку сондата што се пренесува преку ендоскоп. Сондата се поставува на одредено растојание од лезијата на крварење, а гасот на аргонот се испушта јонизиран со висок напон (12). Високофреквентната електрична струја потоа се спроведува низ млазот на гас, што резултира со коагулација на лезијата на крварење на другиот крај на млазот. Бидејќи не се прави физички контакт со лезијата, постапката е безбедна (13) и може да се користи за лекување на крварење во делови од гастроинтестиналниот тракт со тенки ѕидови, како што е цекум. Длабочината на коагулација обично е само неколку милиметри. АПК се користи за третирање на следниве лезии: ангиодисплазии во ГИ тракт, гастрична антрална васкуларна ектазија, постирадијациски проктитис, рак на езофагусот и др. (14).

Многубројни студии ја даваат подршката за ефикасност и сигурност на АПК во клиничката пракса во споредба со други техники (2).

Хируршка ресекција: Оваа метода е индицирана само кај пациенти со животно загрозувачко крвавење, голема потреба од трансфузии и точно утврдено место на крвавење.

Медикаментозна терапија: Хормонска терапија со естрогени (+прогестерон), инхибитори на ангиогенезата (талидомид) и соматостатински аналози (октреотид) (15,16).

Цели на трудот: Да се утврди стапката на рецидивни крвавења кај пациенти со крвавечки ангиодисплазии во горните партии на ГИТ третирани со АПК и инјекциската терапија со раствор на адреналин и полидоканол.

Материјал и методи: Студијата вклучува вкупно 50 пациенти над 18 години. Критериум за вклучување во студијата е ендоскопски потврдени една или повеќе крваречки ангиодисплазии во горните партии на

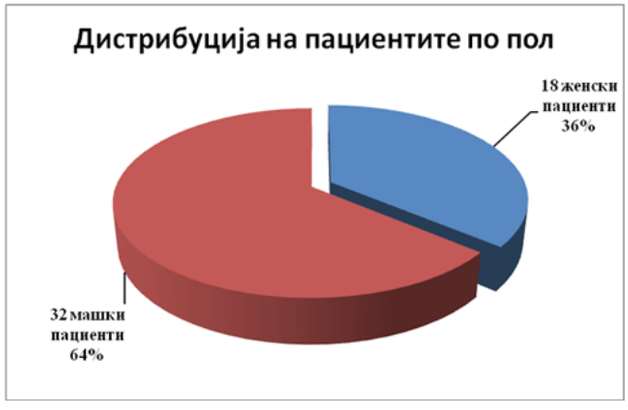
ГИТ со манифестно крварење. Вкупно 35 пациенти се третирани со (АПК), а останатите 15 со инјекциска терапија со раствор на адреналин и полидоканол. Двете тераписки опции се реализираа со ендоскопски пристап.

Првата група на пациенти се третираше со АПК во тек на горнодигестивна ендоскопија, со примена на јачина од 30W и проток од 1-2 L/min. Втората група беше лекувана со инјекциска терапија со раствор на адреналин и 1,5% раствор на полидоканол, аплицирани во и околу самата ангиодисплазија, во количина од максимум 20 мл раствор на адреналин и 1-2 мл раствор на полидоканол, со примена на игла за ендоскопска хемостаза. Пациентите се следеа 6 месеци во тек на 4 визити, и тоа во нулта точка и по 4, 8 и 24 недели. На втората и третата визита се направи ендоскопска контрола.

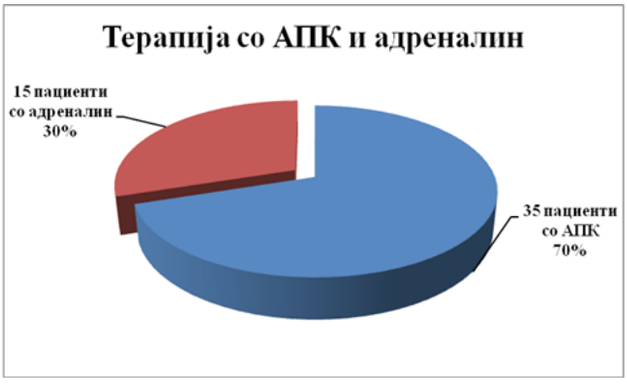
Податоците беа статистички обработени со (SPSSInc., Chicago, IL, САД) со употреба на средна вредност ± стандардна девијација (SD) со 95% (CL), Chi-squere test за квалитативните белези и Student's t и Mann–Whitney-u-test за нумеричките белези. Веројатност (p) со вредност < 0.05 се смета за статистички значајна.

Резултати:

Испитани се вкупно 50 пациенти на возраст од 18 до 64 години. Од нив 32 (64%) машки пациенти и 18 (36%) женски пациенти лекувани на Универзитетската клиника за Гастроентерохепатологија во Скопје во тек 2 години со средна возраст од 55 годни (графикон 1).



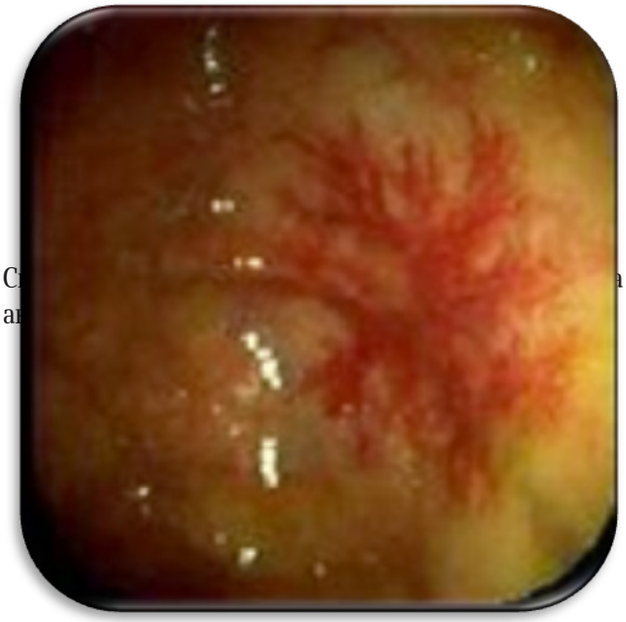
Графикон 1. Дистрибуција на пациентите по пол.



Графикон 2. Дистрибуција на пациентите спрема терапискиот пристап АПК и адреналин

Број на пациенти	Локализација на ангиодисплазијата
33 пациенти	желудник
17	Желудник и дуоденум

Табела број 2. Локализација на ангиодисплазиите



Слика бр.1 Ендоскопски поглед на ангиодиспластична промена кај наш пациент од ендоскопија на горен ГИТ.

Графикон бр.3 Стапка на рецидив со несакани лезии (улкуси).

Направен е Mann-Whithey test p<0,01.

Статистички значајна е стапката на рецидив со крварења кај пациентите третирани со адреналин.

Дискусија:

Иследени беа вкупно 50 пациенти со крварење од горен гастроинтестинален тракт и дијагностицирана е ангиодисплазија. Во однос на дистрибуцијата на пациентите по пол, поброjни беа пациентите од машки пол. Од вкупно 50 пациенти, кај 35 пациенти ангиодисплазиите беа третирани со агрон плазма, а кај 15 пациенти со адреналин. Средната возраст на пациентите 55 години се совпадна со пдатоците од литературата (2).

Се утврди помала стапка на рецидиви на крвавењето кај групата на пациенти кои беа третирани со агрон плазма во споредба со инјекциската терапија со раствор на адреналин и полидоканол, што се совпаѓа со податоците од литературата (2). Во друга студија не е докажана разлика во третманот меѓу конзервативната терапија и терапија со АПК (15,17). Според локализацијата, поголем број на пациенти имаа ангиодисплазии на желудник 66% в.с.34%, што се совпаѓа со податоците од литературата (17,18).

Првата контролна ендоскопија кај сите пациенти третирани со агрон плазма беше со уреден наод. Стапката на рецидивни крварења со несакани лезии (улкуси) беше статистички значајна кај пациентите кои беа третирани со адреналин p<0,01. Повеќе рецидивни крварења беа уочени кај пациентите третирани со адреналин (19-21).

Во однос на анемизирањето, средните вредности на хемоглобинот после интервенцијата беа статистички значајно повисоки кај пациентите кои беа третирани со агрон плазма. Во студии од литературата е докажан бенефитот од АПК и намален процент на рецидивни крварења и анемизирање (12). Во ретроспективна студија на Saperas, не е најдена разлика во однос на процентот на пациенти на повторно крварење во споредба со конзервативната терапија 87% наспроти 73% и 74% наспроти (15).

Заклучок: Ендоскопијата е клучна процедура во дијагностицирање и лекувањето на ангиодисплазиите во гастроинтестиналниот тракт. Третманот на ангиодисплазиите на горните партии на ГИТ со агрон плазма е сигурна метода и со ниска стапка на несакани ефекти и висок степен на тераписка ефикасност (22). Во нашата студија потврдивме помал степен на рециидивантни крвавења кај пациентите третирани со аргон плазма коагулација. Денес се препорачува да се користи АПК како прва линија на терапија на крваречките ангиодисплазии (2).

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Profesional paper

WHO ARE DONORS IN BLOOD TRANSFUSION CENTER STRUMICA

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ABSTRACT

Aim: the aim of this study is to compare individual characteristics associated with blood donations in a small transfusion center for two years period.

Material and methods: a total of 1725 volunteers were studied to evaluate their motivation for blood donation in 2017 and 2018. A questionnaire was prepared by our physicians , covering sociodemographic characteristics, history of blood donation and reasons for donate. Motivation was classified as internal- altruism and external motives.

Results: The main motivations were 1036(48%)-altruistic, 734 or 34%- Good for one's health and Free health screen and laboratory test 150 or 6,9% It is shown that 1184 blood donation volunteers (55%) had internal motivation and 321 or 45% had external motivation for donate blood. Internal motivations were higher in women, regular and educated donors.

Conclusion; Internal motives are the main reason for blood donation in our transfusion center. Altruistic messages can be used in recruiting and retaining donors. Many of the donors were motivated by external factors- mainly to improve their own health status, especially in older donors. The blood establishments should intensity their efforts to motivate women and lower educated people to donate blood. Our study suggest that population- based investigations could be a helpful tool to describe donor rates and to guide future recruitment strategies.

Key words: blood donation, Donor, Motivation

INTRODUCTION

Blood transfusion is a fundamental and requisite part of any National Health Service. Human blood is an essential element of human life and there are no substitutes. Human blood is rare, valuable and very much in need. The need for blood and blood products is being felt more than ever as the population grows. Because, the only source of supply is the blood donor, motivating and retaining donors is the only way to meet this need. Motivation of blood donors is one of the greatest challenges faced by the blood collection facilities today. Motivation is a compelling force of activity which is directed towards meeting personal needs or goals. Everyone who wants to donate, has a specific motivation. Some researches show that there are differences in the factors that motivate first-time donors with respect to that in repeat donors. At the first donation, external factors such as social pressure by peers or friends are important factors in decision to donate, but become less important with repeat donation. Internal factors such as a desire to help others, a sense of duty or desire the help to Red Cross, become more important over time. The purpose of this study is to investigate the motivational factors of our blood donors in our region with regard to their demographic characteristics and history of blood donation.

In 2017 and 2018 year, a total of 2159 blood units were collected in Transfusion department Strumica, which serves about 92000 of population. That means 22 units per 1000 population and that is a good achievement according WHO map on blood donation rates, although an higher level is necessarily (as it is in some developed countries) All of these collected blood units, were obtained from voluntary, non- remunerated blood donors.

MATERIAL AND METHODS

A total of 1725 volunteers were studied to evaluate their reasons for blood donation. All selected volunteers were entered into the study voluntarily and interviewed regardless of whether they were accepted for donation or not. A questionnaire was designed by the physicians, with two different sections.

The first section covered socio-demographic characteristics- age, sex, marital status, education level, job, and personal history of blood donation which means first time donor, repeat donor or regular donor.

The second part consisted of a list of reason for donating. The physician was responsible for interviewing the donor and asking about his/her main reason to donate. The donors usually mention several factors when they were asked about their main motivation. So we decided that the first response will be considered as the main motivation. Motivations were listed as phrases that might be expressed by volunteers as follows:

- Altruistic motive: helping patients, helping others, helping people, moral or social obligation, performing a good job, saving life.
- Health screen: blood group determinate, physical examination of blood pressure and hemoglobin, free laboratory tests.
- Curiosity: no specific reason, want to know how is to donate blood, want to visit a donation center, having a new experience.
- Social pressure: influence of co- workers, friend, boss, family.

At the end of the donor selection interview, the final outcome (accepted or deferred) was recorded in the questionnaire by the physician.

RESULTS

Table 1 show the socio- demographic characteristics and history of blood donation in participants.

Characteristics	Number	%
Sex		
Male	1842	85,3
Female	322	14,7
Age(years)		
18-25	647	29,9
26-45	1187	55
Older than 45	323	14,9
Place		
Urban	1878	87
Rural	281	13
Education		
Basic- primary school	388	17,9
Junior school(as gymnasium)	1036	48
Faculty	518	24
Marital status		
Single	626	29
Married	1533	61
Donor status		
First time	431	20
Repeated	712	33
Regular	1014	47

Regarding employment status, 1455 (67%) were employed, 704 (33%) were unemployed, students were 616 (28%) and retiree 77 (3, 6%).

Table 2 show the most frequent motivation for blood donating.

Helping others	1036 (48%)
Good for one's health	734 (34%)
Curiosity	118 (5, 5%)
Free health screen and laboratory test	150 (6, 9%)
Having a blood donation card	26 (1, 2%)
Social pressure	97 (4, 5%)

The reasons given in the group "good for one's health" were: reduction of blood viscosity, feeling better, mood changes, acne vulgaris, losing weight, treatment of hyperlipidemia. We decided to separate motives into Internal (altruism, helping others) and external (the remaining reasons).

Table 3 show the motivation based on demographic characteristics and history of blood donation

Characteristics	External motivation Number (%)	Internal motivation- altruism Number (%)
Sex		
Male	181 (45, 5%)	1003(54, 5%)
Female	141 (44, 5%)	181 (56, 5%)
Age		
18-25	301 (46, 5%)	346 (53, 5%)
26-45	606 (51%)	581 (49%)
Older than 46	143 (44%)	180 (56%)
Place		
Urban	967 (51, 5%)	911 (48, 5%)
Rural	153 (54, 7%)	128 (45, 3%)
Marital status		
Single	304 (48, 5%)	322 (51, 5%)
Married	752 (49 %)	781 (51%)
Education		
Basic- primary	202 (52%)	186 (48%)
Junior school (such as gymnasium)	524 (50, 5%)	512 (49, 5%)
Faculty	247 (48, 5%)	271 (52, 5%)
Donor status		
First time	214(49, 5%)	217 (50, 5%)
Repeated	363(51%)	349 (49 %%)
Regular	461 (45, 5%)	553 (54, 5%)

So, 1184 blood donation volunteers (55%) had internal motivation and 321 or 45% had external motivation for donate blood. Internal motivations were more significant in women, more dominates in older than 46 years, equally represented in both single and married, more significant in more educated blood donors, and most common in regular donors.

DISCUSSION

The study showed that altruism is the main reason for blood donation in our blood center, which is consistent with similar studies in other countries. There is a significant relationship among altruism and sex, history of blood donation, age and the donor's education level. Women have higher levels of altruistic motivational factor, consequently leading to a greater response to altruistic messages by women. The proportion of female blood donors is significantly lower than male in our transfusion center. So more efforts must be made to attract female donors. Regular donation was also associated with higher levels of altruism. So, our main task is to promote voluntary, regular blood donation without any compensation, with adequate campaigns especially to the predefined target groups.The same thing happened with educated blood donors- althruism is the main motivational factor for their donation, so knowledge about blood donation and altruism seem to be a winning combinations in every transfusion center.Older donors have higher scores of altruistic motivation.There may be a psychological impact in older donors who have a sense of improvement in their general health. One of important factors in our study to donate blood was "Good for one's health"-345 of blood donors. Although it is good that blood donors have a good perception of blood donation, considering blood donation as a means of reduction in cholesterol level, reduction of weight, treatment of acne and so on- has no sound scientific basis .It is possible that some of them are well aware that blood donation is important for patients. Therefore, they continue to donate regularly. It seems that the slogan "good for one's health has a need to be evaluate in near future. Screen health tests represented a main motivational factor in 4, 7% of blood donors. Do they have to control their HIV, Hepatitis B and C, Syphilis status- or they want to control only their blood pressure, hemoglobin level and blood type- is unknown, and it will be subject to next investigation. Simultaneous evaluations of the results of the screening tests and motivational factor could give more valuable information.

CONCLUSION

This study has several strengths. Most of the questionnaires were completed by physicians rather than by blood donors. Results should be compared with the results in other transfusion centers in our country, also and centers in other countries. This study also was an evaluation of motivation in blood donors nationwide. Limitations exists and may influence the final results and conclusion. And conclusion is – that altruistic reasons are the main reason for donation by majority of our blood donors. Most of them are female, regular and high educated donors. Altruistic messages can be emphasized in recruiting and retaining these group. About half of blood donors were motivated by other motivational factors, the main factor being improvement of their health. Understanding blood donor motivations is crucial to improving effectiveness of donor recruitment and retention programs. We have to work hardly and to motivate prospective donors in the

sociocultural settings, both inside the hospital as well as in the community.

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Profesional paper

ECURIA E TUBERKULOZIT SIPAS MOSHES ,GJINISE DHE RAJONEVE E KOSOVE PER PERIUDHEN 2003-2014

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HYRJE

Tuberkulozi është shkaku i nëntë i vdekjeve në mbarë botën dhe shkaktohet nga një agjent i vetëm infektiv qe eshte Mycobacterium tuberculosis. Ekziston një barrë ende e lartë e sëmundjes se Tuberkulozit ne Kosove dhe progresi nuk eshte aq i shpejte sa për të arritur Objektivat e Zhvillimit të Qëndrueshëm për t'i dhënë fund epidemisë globale të tuberkulozit. Kerkimet për diagnostikime të reja, medikamente, regjime të trajtimit dhe vaksinat po përparojnë, por ngadalë. Financimi për kujdesin dhe parandalimin e TB është rritur duke ju falenderuar donatorve për më shumë se 10 vjet, por mungesat e financimit nga shteti ende ekzistojnë. Megjithate perkunder ketyre veshtiresive Tuberkulozi ne Kosove tregon nje trend renjeje

Qëllimi Qëllimi i këtij punimi është prezantimi i ecurise te te semuarve nga Tuberkulozi sipas moshes, gjinise dhe rajoneve gjate periudhes 2003-2014.

Materiali dhe Metoda Ky është një studim retrospektiv i percjellur prej vitit 2003-2014 ne Kosove. Jane perpunuar te gjitha skedat e mjekimit te te semureve me TB ne tere Rajonin e Kosoves, dhe ne studim u perfshine te gjithe te semuret me TB, Nga kartelat klinike te pacienteve eshte mbledhur informacioni: sociodemografik si per moshen, gjinine dhe vendbanimin

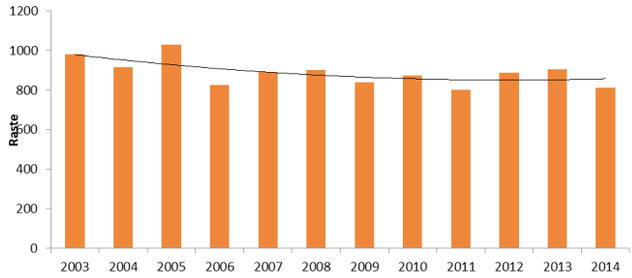
Për analizën e të dhënave është përdorur programi statistikor SPSS 20.0. Variablat e vazhdueshëm janë përmbledhur si mesatare ± deviacionin standard (SD) dhe statistika tjetër deskriptive e tyre. Është përdorur testi Ȼ2 dhe Fisher exact test për krahasimin e përqindjes ndërmjet variablave kategorikë. Per krahasimin e moshes se pacienteve jane perdorur testet jo-parametrike Man Whitney dhe Kruskal Wallis. Vlerësimet pikësore janë shoqëruar me intervalin e besimit 95% CI. Vlera e p ≤0.05 u konsiderua statistikisht e rëndësishme. Të gjitha testet statistikore janë të dyanshme. Për vizualizimin e të dhënave janë përdorur tabela, diagrama dhe grafikë.

REZULTATE DHE DISKUTIMI

Në studim janë përfshirë 10669 pacientë te shperndare sipas viteve dhe te dhenat jane analizuar sipas gjinise moshes dhe rajoneve.

Tabela 1 Karakteristikat sociodemografike te pacienteve

Variablat	N	%
Gjinia		
Femra	5223	49.0
Meshkuj	5446	51.0
Mosha, M (SD)	42.2 (20.6)	
Grupmosha, vite		
≤ 20	1711	16.0
21 – 30	2372	22.2
31 – 40	1558	14.6
41 – 50	1164	10.9
51 – 60	1203	11.3
>60	2661	24.9
Vendbanimi		
Fshat	6283	59.0
Qytet	4386	41.0
Vitet		
2003	980	9.2
2004	916	8.6
2005	1033	9.7
2006	827	7.8
2007	891	8.4
2008	900	8.4
2009	837	7.8
2010	875	8.2
2011	803	7.5
2012	889	8.3
2013	906	8.5
2014	812	7.6



Ne baze te dhenave te prezentuara ne tabelen dhe diagramin 1 numrin e te semuarve nga tuberkuloza sipas viteve, numri me i madhe i rastevete ka qene ne vitin 2003 dhe 2005 derisa numri me i vogel 2011 dhe 2014 çka tregon se Tuberkulozi shenon renje ne Kosove nga viti ne vite.

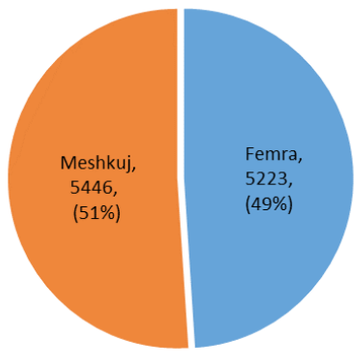


Figura 2. Shpërndarja e rasteve sipas gjinise

Nga numri i pergjitheshem i te semuarve 5223 ose 49% prej tyre ishin femra dhe 5446 ose 51% meshkuj pa ndryshim statistikisht të rëndësishëm ndërmjet tyre (Mann-Whitney p=0.1) Raporti i pacientëve meshkuj/ femra ishte 1 : 1.04. Nese i krahasojm te dhenat tona me vende tjera ato plotesisht perputhen me te dhenat e shteteve ne rajon (Shqiperi2 Maqedoni5, Bosnie e Hercegovine6, Serbi4 dhe Kroaci3)

Tabela 2 Statistika e permbledhur e moshes

Variablat	M	SD	Min	Q1	Median	Q3	Max
Total	42.0	20.6	0	24.0	38.0	60.0	101
Femra	42.3	20.5	1	24.0	38.0	61.0	101
Meshkuj	41.8	20.6	0	24.0	39	60.1	98

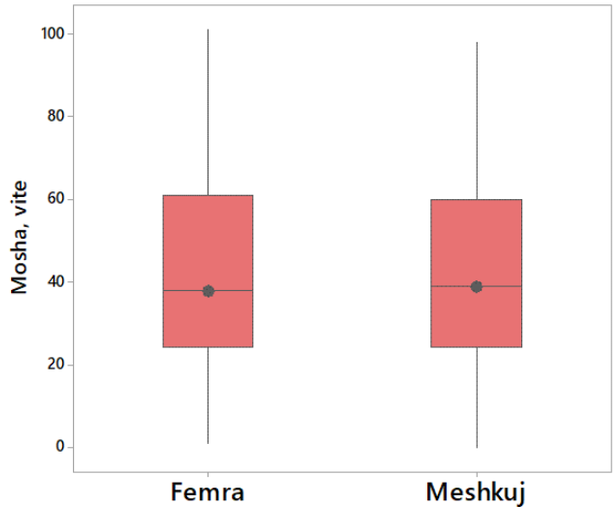
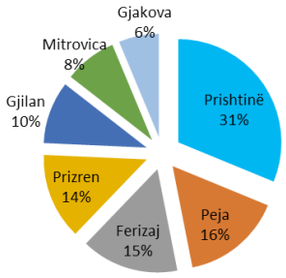


Figura 3. Krahasimi i moshës së pacientëve sipas gjinisë

Mosha mesatare e meshkujve eshte 41.8 (±20.5) vjeç (rangu 0–98 vjeç) ndersa mosha e femrave eshte 42.3 (±20.6) vjeç (rangu 1–101 vjeç) pa ndryshim statistikisht të rëndësishëm ndërmjet tyre (Mann-Whitney p=0.1)

Edhe pse te gjitha grup-moshat janë të rrezikuara me tuberkulozë verehet mbizoterimi i rasteve ne grupmoshen 21-30 vjeç me 22.2% te totalit dhe ne grupmoshen >60 me 24.9% te totalit, me ndryshim statistikisht te rendesisehm me grupmoshat e tjera (p<0.001) Pra, tuberkulozi ne Kosove paraqitet më shume te personat me moshë mbi 60 vjeç, sikurse edhe në vendet e zhvilluara evropiane.



Verehet qe numri me i madh i rasteve eshte nga Rajoni i Prishtines 3331 (31.2%), me ndryshim statistikisht te rendesishem me Rajonet e tjera (Ɛ2=30.7 p<0.01), ndjekur nga Rajoni i Pejes me 1674 (15.7%) raste, Rajoni i Ferizajit 1632 (15.3%), Prizrenit me 1444 (13.5%) raste, Gjilan 1044 (9.8%), Mitrovica 875 (8.2%) dhe Gjakova 669 (6.3%)

Tabela 3. Numri i rasteve dhe incidence e TB sipas Rajoneve (raste/100000)

Qyteti	Popullsia	N	Incidenca (raste/100000)
Prishtinë	201214	3331	1655.5
Peja	97481	1674	1717.3
Ferizaj	109885	1632	1485.2
Prizren	179868	1444	802.8
Gjilan	91009	1044	1147.1
Mitrovica	85122	875	1027.9
Gjakova	95548	669	700.2

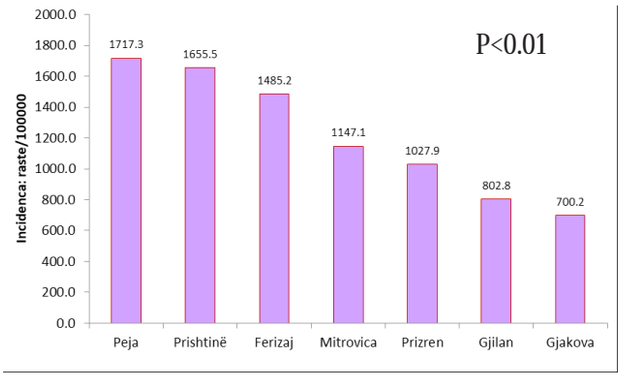
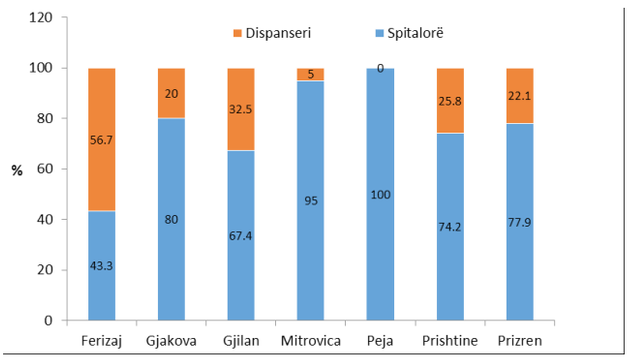


Figura 3. Incidenca e TB sipas Rajoneve (raste/100000)

Nga te dhenat e prezentuara shofim se Incidenca me e larte eshte ne Rajonin e Pejes

Me 1717.3 raste/100000 banore, ndjekur nga Prishtina (1655.5 raste/100000 banore), Ferizaj (1485.2 raste/100000 banore), Mitrovica (1147.1 raste/100000 banore), Prizren (1027.9 raste/100000 banore), Gjilan (802.8 raste/100000 banore), dhe Gjakova (700.2 raste/100000 banore). U gjet ndryshim statistikisht i rendesisehm i incidences se TB sipas Rajoneve (p<0.001).



Edhe sipas Rajoneve mbizoteron trajtimi spitalor kundrejt trajtmit ambulator, perveç Rajonit te Ferizaj (p<0.01). Ne rajonin e Pejes nuk e kemi asnjë rast qe eshte trajtu ne

Dispanseri meqe Rajoni i Ferizajit nuk ka Spital.

PERFUNDIMET

Në vazhdimësi kemi një rënie të vazhdueshme të numrit të të sëmurëve nga tuberkulozi për periudhën e analizuar nga viti 2003-2014,

Gjithesej ne studim janë përfshirë 10669 pacientë prej tyre 49% ishin femra dhe dhe 51% meshkuj. Raporti i pacientëve meshkuj/femra ishte 1 : 1.04

Mosha mesatare e meshkujve eshte 41.8 (±20.5) vjeç (rangu 0–98 vjeç) ndersa mosha e femrave eshte 42.3 (±20.6) vjeç (rangu 1–101 vjeç) pa ndryshim statistikisht të rëndësishëm ndërmjet tyre (Mann-Whitney p=0.1)

Verehet mbizoterim i rasteve ne grupmoshen 21-30 vjeç me 22.2% te totalit dhe ne grupmoshen >60 me 24.9% te totalit, me ndryshim statistikisht te rendesisehm me grupmoshat e tjera (p<0.001)

Numri me i madh i rasteve eshte nga Rajoni i Prishtines 31.2%, me ndryshim statistikisht te rendesishem me Rajonet tjera (Ɛ2=30.7 p<0.01), ndjekur nga rajoni i Pejes me 15.7% raste, rajoni i Ferizajit 15.3%, Prizreni me 13.5% raste, Gjilan 9.8%, Mitrovica 8.2% dhe Gjakova 6.3% raste.

Në Kosovë, tuberkulozi edhe pse në rënie të incidencës nga viti në vit, ende paraqet një vatër endemike tuberkulare.

Incidenca me e larte eshte ne Peje 1717.3 raste/100000 banore, ndjekur nga Prishtina (1655.5 raste/100000 banore), Ferizaj (1485.2 raste/100000 banore), Mitrovica (1147.1 raste/100000 banore), Prizren (1027.9 raste/100000 banore), Gjilan (802.8 raste/100000 banore), dhe Gjakova (700.2 raste/100000 banore). U gjet ndryshim statistikisht i rendesisehm i incidences se TB sipas rajoneve (p<0.001).

Nuk verehet ndryshim sinjifikant ndermjet rajoneve persa i perket i trendit te rasteve ne vite (p=0.2).

Edhe sipas qyteteve mbizoteron trajtimi spitalor kundrejt trajtmit ambulator, perveç qytetit te Ferizaj meqe nuk ka spital rajonal dhe te semuret kryesisht trajtohin ne QKUK si dhe ne spitalet tjera rajonale .

REKOMANDIMET :

1. Diagnostikimi i hershem, perpunimi i kontaktit dhe zbulimi i rasteve te TB me kohe do te ndikoj dukshme ne zvogelimin e numrit te rasteve me tuberkuloz.
2. Veprimtaria edukativo shëndetësore per parandalimin dhe kontrollin e tuberkulozit duhet te realizohet në mënyre të vazhdueshme dhe sistematike në institucione shëndetësore dhe ato jo shëndetësore si dhe duhet te gjinden mekanizmat që do të shpien deri tek qëndrueshmëria formale e kësaj veprimtarie.

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Profesional paper

SALVAGE RADICAL CYSTECTOMY WITH ILEAL CONDUIT DIVERSION (BRICKER PROCEDURE) AS A METHOD OF CHOICE IN THE TREATMENT OF HIGH GRADE INVASIVE CARCINOMA OF THE URINE BLADDER

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ABSTRACT

Introduction: Radical cystectomy and lymph node dissection is considered as the gold standard treatment for muscle invasive urothelial carcinoma of the urine bladder. According to the EAU guidelines, radical cystectomy should be performed in patient with T2-T4a, N0-Nx, M0 stage of bladder cancer. If the patient is not undergoing neoadjuvant chemotherapy, radical cystectomy should be performed within 12 weeks of diagnosis/staging. For the patients who had preoperative radiation therapy the usual time between the end of the radiation and the cystectomy is from 3-6 months.Unfortunately significant percentage of the patients in our region has been still diagnosed with high grade invasive carcinoma in their third and fourth stadium, combined with continuous haematuria, bilateral hydronephrosis and pain in the lower abdomen because of the neoplastic infiltration in the perivesical tissue. The salvage radical cystectomy with ileal conduit urinary diversion (Bricker procedure) is indicated in nonrespondin patients to chemo and radiation therapy, multiple recurrences of the tumor, acute massive bleeding and patients with inoperabile vesico-vaginal or vesico-rectal fistulas as definitive surgical solution after the radiation therapy.

Materials and Methods: Radical cystectomy was performed in 46 patients at the Department of urology, General City Hospital "8th of September" –Skopje, for the past three years. The postoperative pathohistological findings revealed: 4 patients with stage I (pTa pNoMxG2), 13 patients with stage II (6 with pT2aNoMo, 5 with pT2bNoMo and 2 wih pT2cNoMx-with infiltration in the prostate gland), 22 patients with stage III (13 with pT3aNoMo, 6 with pT3bNoMo, 3 patients with pT4aNxMx G3) and 7 patients with stage IV pT4bN1M1.

Results: Salvage radical cystectomy with ileal conduit urinary diversion (Bricker procedure) was performed in 9 patients (19,56%). From those: 2 patients with stage II were operated because of massive haematuria, in 5 patients with stage IV radical cystectomy was performed because of severe pains in the lower abdomen, haematuria, bilateral hydronephrosis gr 3-4 with high level of creatinin, urea and potassium and in 2 female patients the radical cystectomy was performed because of post-irradiation inoperable vesico-vagino-rectal fistula. Average follow up of the patients was 2,63 years.

Overall three years survival is 95,6% (44 patients) with postoperative mortality rate 4,34% (2 patients). Three years survival of the patients with salvage cystectomy is 88,9% (8 patients) with postoperative mortality rate 11,1% (1 patient).

Conclusion: Salvage radical cystectomy with ileal conduit urinary diversion is still the best option as life saving surgical solution in patients with acute massive haematuria, block infiltration of the neoplastic process combined with bilateral obstruction of the ureters and patients with inoperable post irradiation vesico-vaginal or vesico-rectal fistulas.

Keywords: salvage cystectomy, radical cystectomy, muscle-invasive bladder cancer, ileal conduit urinary diversion

INTRODUCTION

Bladder cancer is the ninth most common diagnosed cancer worldwide, with more than 380,000 new cases each year, more than 150,000 deaths per year, and an estimated male-female ratio of 3.8 : 1.0. (1)

Radical cystectomy (RC) and lymph node dissection is considered as the gold standard treatment for muscle&invasive urothelial carcinoma of the urine bladder. According to the EAU guidelines, radical cystectomy should be performed in patient with T2-T4a, N0-Nx, M0 stage of bladder cancer. If the patient is not undergoing neoadjuvant chemotherapy, radical cystectomy should be performed within 12 weeks of diagnosis/staging. For the patients who had preoperative radiation therapy the usual time between the end of the radiation and the cystectomy is from 3-6 months. Other indications for RC include recurrent superficial tumours, BCG-resistant Tis, T1G3 and papillary tumors that cannot be controlled with TURB and intravesical therapy.

Standard radical cystectomy in men includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional lymph nodes. Standard RC in women includes removal of the bladder, entire urethra , adjacent vagina, uterus, distal ureters, and regional lymph nodes.

Comparing with the elective radical cystectomy, the salvage radical cystectomy (SRC) is indicated as an extorted life saving surgical method in patients with recurrent macrohaematuria with secondary anemia, recurrent severe pains, non-responders to conservative therapy, recurrence after bladdersparing treatment, non-urothelial carcinoma, patients with muscle invasive bladder cancer (MIBC) combined with obstructive bilateral hydronephrosis and it can be also used as a definitive solution in patients with unsolvable vesico-vaginal, vesico-rectal or vesico-vagino-rectal post irradiation fistulas.

The SRC should be also distinguished from the palliative cystectomy where the surgical intervention is limited only on cystectomy (without lymphadenectomy, prostatectomy, removal of the seminal vesicles and the distal ureters).

Most of the issued articles concerning SRC confirm this method as a solution for patients not responding to neoadjuvant radiation therapy (2,3,4), patients with massive bleeding of the bladder cancer (5) and patient with failed partial cyctectomy (6).

Unfortunately significant percentage of the patients in our region has been still diagnosed with high grade invasive carcinoma in their third and fourth stadium, combined with continuous haematuria, bilateral hydronephrosis and pain in the lower abdomen because of the neoplastic infiltration in the perivesical tissue.

The most common urinary diversions described in the available urology articles, used within the radical cystectomy are: ileal conduit, orthotopic bladder and ureterocutaneostoma (7).

MATERIALS AND METHODS

Radical cystectomy was performed in 46 patients at the Department of urology, General City Hospital "8th of September" - Skopje, for the past three years. The postoperative pathohistological findings revealed: 4 patients with stage I (pTa pNoMxG2), 13 patients with stage II (6 with pT2aNoMo, 5 with pT2bNoMo and 2 wih pT2cNoMx-with infiltration in the prostate gland), 22 patients with stage III (13 with pT3aNoMo, 6 with pT3bNoMo, 3 patients with pT4aNxMx G3) and 7 patients with stage IV pT4bN1M1.

AIMS

1. Determining the indications for salvage radical cystectomy in our patients with muscle invasive carcinoma of the urine bladder.
2. Determining the most useful urinary diversion during the radical cystectomy.
3. Determining the efficacy of the surgical versus conservative treatment of the patients with high grade muscle invasive carcinoma of the urine bladder.
4. Determination of the survival rate after salvage radical cystectomy in our patients.

Results: From 46 radical cystectomies performed at our Urology Department, salvage radical cystectomy with ileal conduit urinary diversion (Bricker procedure) was performed in 9 patients (19,56%). From those: 2 patients with stage II were operated because of massive haematuria, in 5 patients with stage IV radical cystectomy was performed because of severe pains in the lower abdomen, haematuria, bilateral hydronephrosis gr 3-4 with high level of creatinin, urea and potassium and in 2 female patients radical cystectomy was performed because of post-irradiation inoperable vesico-vagino-rectal fistula.

The postoperative patohistological findings revealed the following stages of the bladder cancer: stage I - 8,69%, stage II – 28,2%, stage III – 43,53% and stage IV – 19,56% of the patients underwent radical cystectomy. (Diagram 1.)

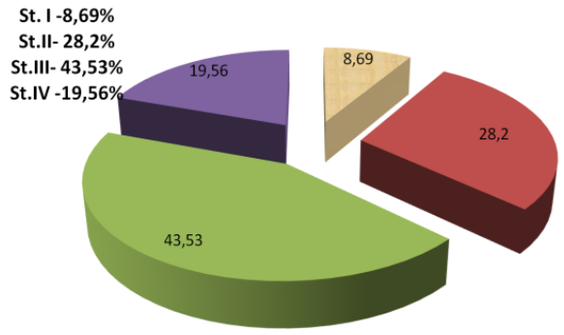


Diagram 1. Percentage of patients with different stage of the bladder cancer

Average follow up of the patients 2,63 years.

Overall three years survival is 95,6% (44 patients) with postoperative mortality 4,34% (2 patients). Three years survival of the patients with salvage cystectomy is 88,9% (8 patients) with postoperative mortality 11,1% (1 patient).

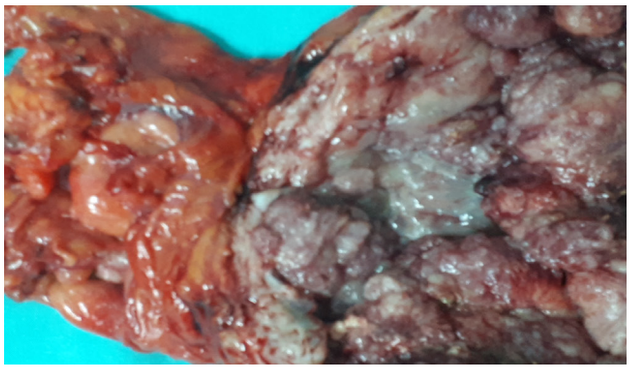
Postoperative pathohystological findings

Pathohystology findings	Number of patients
Stadium I (pT1 pNo pMx G1)	4 (9,09%)
Stadium 2 (pT2a No Mo G2)	6 (13,6%)
Stadium 2 (pT2b pNo pMx G2)	6 (13,6%)
Stadium 2 (pT2b pNo pMx G3)	1 (2,27%)
Stadium 3 (pT3a pNx Mx G3)	13 (29,5%)
Stadium 3 (pT3b pNo pMo G3)	4 (9,09%)
Stadium 3 (pT4a pNx pMx G3)	3 (6,81%)
Stadium 4 (pT4b pN1 pM1 G4)	7 (15,9%)
Overall:	44

Table 1. Pathohystologycal stages after the radical cystectomies

Salvage radical cystectomy was performed in 9 patients (19,56%) without preoperative neoadjuvant therapy (radiation or chemotherapy). Urinary diversion with ileal conduit was performed in all cases. The final effect of this procedure was: interruption of the massive bleeding, solving the bilateral hydronephrisis and the obstructive renal failure, improvement of the general condition of the patient and definitive solution of the unsolvable vesico-vaginal and vesico-vagino-rectal fistulas.

In all of the cases massive neoplastic infiltration was found in the prostate and the seminal vesicles (picture1).



Picture 1. Massive neoplastic infiltration in the prostate and seminal vesicles

Postoperative mortality rate within the patients with salvage RC is 11,11%.

Three years survival of the patients undergone salvage radical cystectomy was 89,9%.

DISCUSSION

For the past two decades the MIBC has been treated either with radical cystectomy eather with conservative therapy (called tri-modality approach: TURB, radiation and chemotherapy). Comparing these two different approaches it seems that the radical cystectomy with pelvic node dissection gives better results in overall 5 years survival especially within the patients under 69 years of age (8). The probability of the survival after the radical cystectomy is determined by the pathologic stage of the disease and accompanied co-morbidities of the patient.

The percentage of the salvage radical cystectomy (SRC) versus elective RC varies in many studies from 3,1% (9) to 29% (10). Comparing with this data in our group of operated patients SRC was performed in 19,56%.

The type of the urinary diversion whilst SRC also varies depending on: the decision of the urologist, local intraoperative finding and the general condition of the patient. Some urology centers prefer orthotopic bladder, some use ureterocutaneostoma and others prefer ileal conduit (Bricker procedure). In our case ileal conduit was performed in 100%. Orthotopic bladder was avoided because all of the patients had infiltration in the bladder neck and the prostate. Ureterocutaneostoma was not performed to avoid the postoperative stenosis and prolaps of the stoma. The result was normal uroflow without any postoperative complications.

The mortality rate during SRC also varies according to

different urology departments from 3,5% to 16% (10). In our examined group the mortality rate was 11,11%.

Three years survival after the SRC in our group is 88,9% of the patients. This data confirms the radical cystectomy with ileal conduit as an effective and recommended method of surgical solution for MIBC followed with severe pain, acute bleeding, ureteral obstruction with renal impairment and voiding symptoms such as urgency and urge incontinence.

CONCLUSIONS

1. Salvage radical cystectomy as a term should involve not only cystectomy after unsuccessful radiation or chemotherapy, but a cystectomy that is forced out as an urgent surgical solution by a vital indication and cystectomy perform for improvement of the quality of life of patients with a high stage of bladder cancer.
2. "Salvage" radical cystectomy is definitely the only solution in patients with invasive carcinoma of the urine bladder accompanied with:
   - massive haematuria,
   - two-sided obstructive hydronephrosis with renal impairment,
   - severe voiding disorders due to reduced capacity of the urine bladder,
   - inquireable severe pain in the suprapubic region and
   - surgical insolvable vesico-vaginal and vesico-vagino-rectal fistulas.
3. Radical cystectomy with ileal conduit in our current practice has proven to be the best definitive surgical solution for saving patient's life due to the relatively low mortality (11.11%), good three-year survival (88.9%) as well as providing better quality of life of the patient.
4. If cystectomy can not be performed due to local malignant infiltration, according to our experience so called "By pass" urinary derivation with ileal conduit proved to be the most adequate permanent surgical solution compared to other derivations (permanent nephrostoma, single or double-sided ureterocutaneousostomy, etc.)
5. The high percentage of SRC (19.56%) in our study, compared with other studies where the percentage ranged from 3.1 to 5.3% and the high percentage of diagnosed patients with high stage of MIBC (63%) in our region, points to the need to promote screening diagnostics for early detection and prevention of these malignant diseases in our healthcare system.

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Profesional paper

REVIEW OF GRAFT APPLICATION IN RHINOPLASTY

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SUMMARY

Grafts are often part of primary rhinoplasty but they are especially widespread in secondary rhinoplasty, being the sine qua non in many cases. This paper reviews the use of grafts in rhinoplasty, describes modern trends in this field and presents pictures of some of our cases regarding this issue. Cartilage is the most commonly used graft, but other tissues such as fascia and bone may also serve the purpose. The usual donor sites for cartilage grafts are the septum, ear, and ribs, while fascia is usually harvested from the deep temporal fascia. There are numerous types of graft, primarily cartilage grafts, which vary depending on the shape, method of preparing, purpose of use, etc. Grafts taken from one's own tissues have shown to be advantageous over all other types of grafts or prostheses. The development of various grafts and an increasing of number of complicated problems which they have solved, have revolutionized rhinoplasty.

KEY WORDS: grafts, rhinoplasty, cartilage, nose

I

NTRODUCTION: Grafts are widely used in rhinoplasty for solving a wide range of problems. Although this procedure can be used in both open and closed rhinoplasty, an open rhinoplasty approach offers a better access to and optimal exposure of the nasal structures, making them more suited for open rhinoplasty. Closed rhinoplasty is predominant in Macedonia and the use of graft has limited application. While on the one hand grafts are being strictly defined in terms of donor sites, harvesting and the purpose of their use, on the other hand there has been an increase in the number and the types of grafts used, as well as the problems solved with their use. Grafts can correct both aesthetic and functional nasal problems. They have become a powerful resource in correcting tissue defects related to the nasal root, nasal dorsum, septum, nostrils, upper and lower alar cartilage as well as various other defects and deformities. The use of grafts requires a good knowledge of nasal anatomy and experience in rhinoplasty operations.

ALLOPASTS, AUTOGRAFTS AND HOMOGRAFTS (ALLOGRAFT) IN RHINOPLASTICS: Grafts used in rhinoplasty are different. The history of rhinoplasty includes cases of alloplasts from various materials as well as autografts and allografts, which have stood the test of time and confirmed the superiority of biological material

to non-biological material as well as superiority of grafts from own tissues to those obtained from other donors. In search for simple solutions and in order avoid additional surgical manipulation to harvest and shape them, different firms have invested in the production of prostheses from numerous materials as a replacement for grafts, with a view to solving different aesthetic and functional nose problems. Unlike in many other parts of the body (vascular prostheses, hernia mesh, articular prosthesis, etc.), many non-synthetic and synthetic materials used in rhinoplasty, including biocompatible materials (goretex, mersilene, etc.), used so far in rhinoplasty have not yielded satisfactory results, primarily due to two frequent and serious complications: infection and extrusion of the prosthesis. The main disadvantage of allografts (homografts) compared to autografts lies in their absorption over time. This is especially true in the case of grafts harvested from cadavers.

TYPES OF GRAFTS BASED ON THE TISSUE AND DONOR SITE: A variety of tissues can be used as grafts in rhinoplasty. They can be of a single type tissue or composite grafts. Cartilage is the most used graft in rhinoplasty (Photo. 1a, b, c) but other tissues such as fascia, bone, perichondrium or dermis are used as grafts as well. Composite grafts are usually composed of cartilage and skin (chondrocutaneous) or cartilage and ribs (osteocartilaginosis).

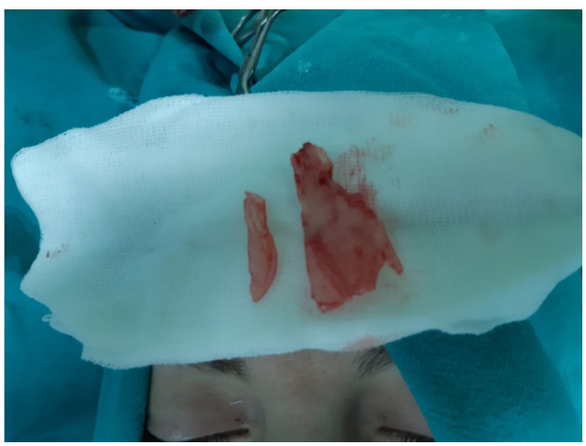


Photo 1a – nasal septum cartilage graft

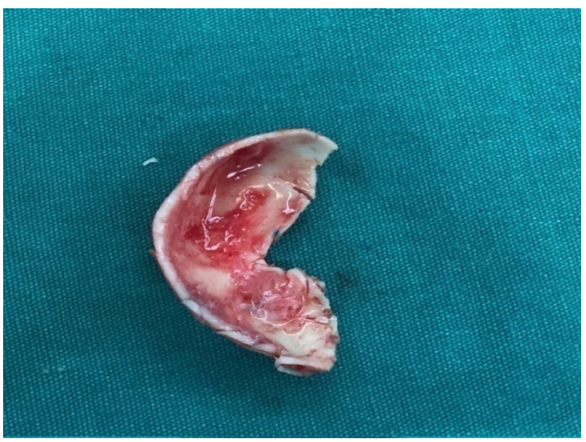


Photo 1b – auricule cartilage graft

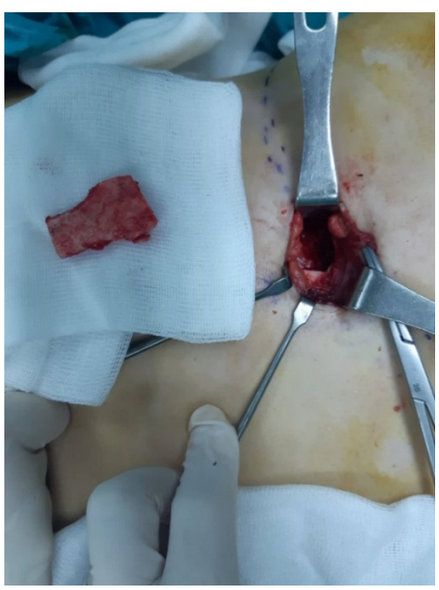


Photo 1c – rib cartilage graft

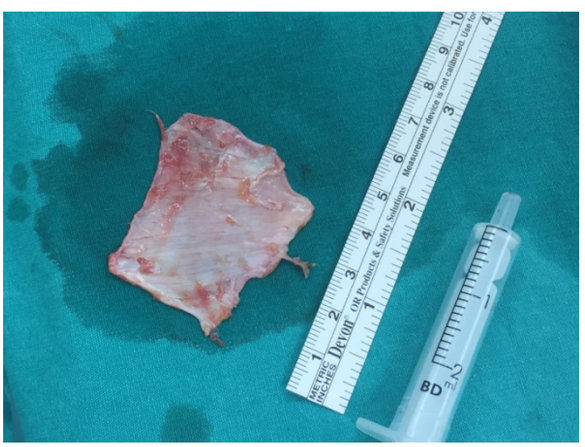


Photo 1d – deep temporal fascia graft

In most cases, the cartilage is harvested from the nasal septum. In other cases, the ear serves as the donor site. Auricular concha is often used as a donor site for harvesting cartilage (or even for chondrocutaneus composite graft) from the ear, because it offers the possibility of harvesting more material as well as gaining the more acceptable aesthetic result. Ribs provide more abundant cartilage material. They serve as a cartilage donor site especially in complicated cases of secondary rhinoplasty, where grafts are the main weapon of correction, and usually the septum has already been used as a cartilage donor area during the first surgery. In some cases, the resected portions of the lower alar cartilages can be used as grafts to correct the tip of the nose.

The ribs, iliac crest and epicranium serve as bone grafting sites, with ribs being mostly used for this purpose. In rare cases, the rib pericondrium can also be taken as a graft.

Deep temporal fascia above the ear is the most common fascia used a for grafting, but there are surgeons who also harvest fascial material from the aponeurosis of the external oblique muscle or rectus abdominis muscle.

Dermis has limited use as graft in rhinoplasty. In cases where a small dermal graft is needed, the retroauricular portion is used as a donor area, because the cicatrix is covered by the auricula and contains the thinnest skin on the human body after eyelid; where larger dermal grafts are required, they are harvested from the suprapubic region.

HARVESTING:

NASAL SEPTUM (Photo 2a) constitutes one of the most common donor sites for cartilage grafts, especially in primary rhinoplasty. Its harvesting should be performed carefully in order to avoid septum perforation. Infiltrating local anesthesia in advance enables easier tissue separation provided by hydrodissection and local vasoconstriction that stops bleeding. Harvesting of the cartilage graft is carried out through incision of the mucosa and its dissection from the septum cartilage on both sides followed by its separation from the perpendicular plate of the ethmoid bone and vomer. When removing the cartilage graft from the nasal septum, a portion of the dorsal and caudal part of the nasal septum cartilage, of at least 1 cm, should always be preserved in the shape of the reversed letter L. For this reason, any removal of cartilage graft from the septum should be done after resection of the dorsum and caudal part of the septum is completed. Otherwise, the structural stability of the septum may be compromised. After the graft is harvested, the site should be compressed in order to avoid the formation of hematomas and other complications such as adhesion of the mucosa of the septum to the conchae nasales. Some surgeons suture the mucosa of both sides of the septum where the cartilage graft was taken or use silicastic splints for compression of the site. We have had good results using tampons with Vaseline gauze.

Photo 2a – nasal septum cartilage graft harvesting

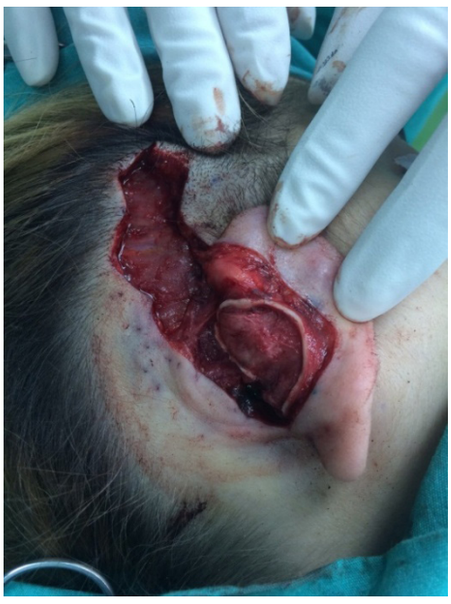


Photo 2b – Auricular concha after cartilage harvesting

EAR serves as a donor site for harvesting cartilage or composite grafts, cartilage and skin. In case of cartilage grafts, usually the incision is made in the retroauricular sulcus in order to cover the incision. After local anesthesia administration, the skin is incised and concha is identified from behind and excised, in order to be separate it from the rest of the ear. After meticulous hemostasis, the concavity where the cartilage was removed is compressed with a gauze and the skin is sutured. Incisions in the front of the ear leave more visible scars. They are used to harvest chondrocutaneus composite grafts from concha or from the part under the helix root.

RIBS serve as donors for cartilage, bone or bone-cartilage (osteocartilaginous) grafts. As a rule, cartilage is harvested after administration of local anesthesia, which is followed by tissue dissection and exposure of the fifth and sixth costal cartilage via inframammary incision, or exposure of the seventh, eighth and ninth costal cartilage via subcostal incision. Following subcutaneous dissection, the fifth (or the sixth) rib is initially separated from the fascia and surrounding tissues and then dissected subchondrially, in contrast to the ninth rib which is dissected suprachondrially. Perichondrium can be left in place or can be used as a graft. Care is taken to avoid pneumothorax and to make sure that this did not happen, at the end of the graft harvesting one should perform the test by filling the wound with saline while the anesthesiologist is maximally expanding the lung. The use of rib cartilage grafts is widespread especially in the complicated operations of secondary rhinoplasty.

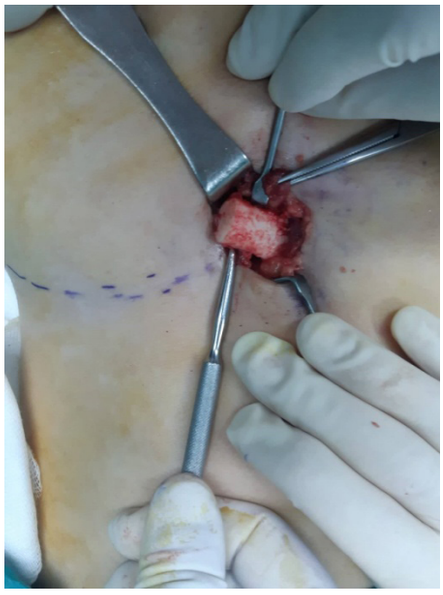


Photo 2c – rib graft harvesting

Photo 2d – deep temporal fascia graft harvesting

DEEP TEMPORAL FASCIA is more desirable than other fascial structures due to its survival, haircut coverage, thickness and ease of harvesting. We use a broken line incision in the form of a letter 'v' to retrieve the deep temporal fascia from the scalp above the ear. After local anesthesia infiltration, the skin is cut and subcutaneous tissue is dissected under the superficial temporal fascia, until the deep temporal fascia is reached. After the incision of deep temporal fascia, temporal muscle is seen under the fascia. Fascia can be obtained in different dimensions, as needed. After careful hemostasis, the skin is closed with stitches.

GRAFT APPLICATION AND TYPES OF CARTILAGE GRAFTS: Cartilages are the main 'weapon' among the various tissues used as grafts in rhinoplasty. The variety of harvesting sites, their flexibility, different types, numerous variations of forms and designs of cartilage grafts and the generally good results of correction of aesthetic and functional nasal problems have made them extensively used in rhinoplasty, both primary and secondary. Cartilages are tissue structures with long time survival but their viability is impaired if compressed.

The most commonly used cartilage grafts are: strut grafts (columellar struts and lateral crural grafts), spreader grafts, tip refinement grafts (TRG) and alar rim grafts.

Strut grafts (Photo 3a) are cartilages in rectangular shape, that are placed and stitched between the medial crura to enhance the stability of the columella and the tip of the nose - in the case of columella grafts (most frequently 2-4

mm wide and about 20 mm long), or sutured to the lower lateral nasal cartilages - in order to stabilize these structures (Photo 3b) (usually 3-4 mm by 15-20 mm).

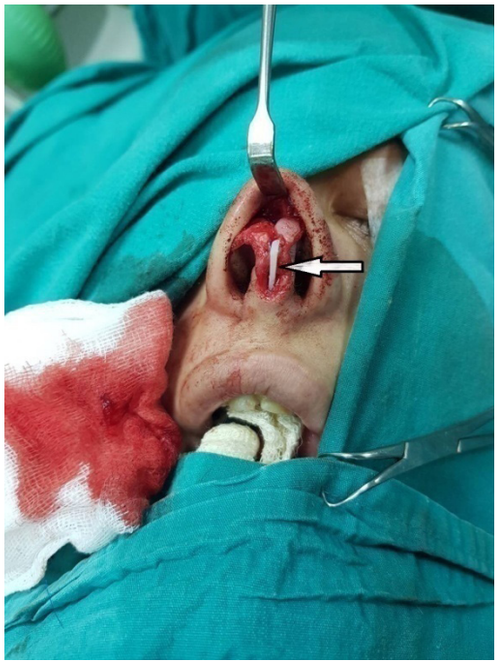


Photo 3a – strut graft

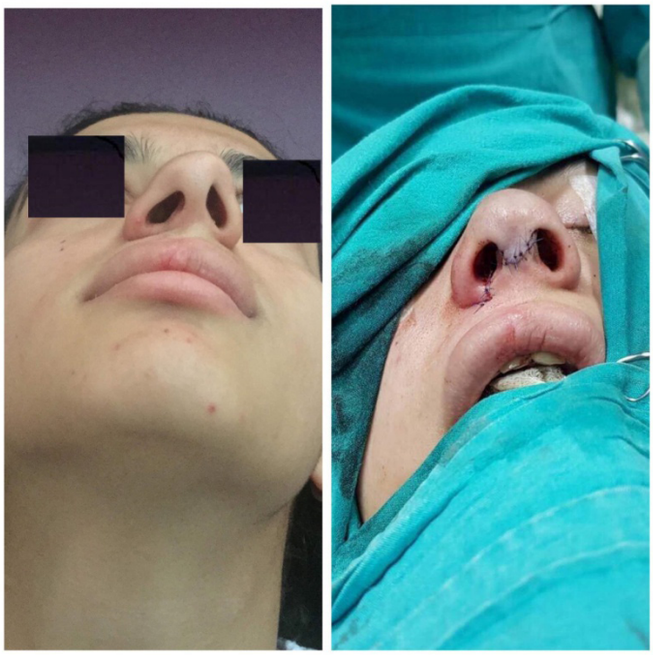


Photo 3b – adjustment of nasal tip deformity with the use of strut graft in a patient with nose deformity and cheilognathoscisis

In a number of cases, after emoving the kyphosis of the nasal dorsum, the closure of the remaining defect (known as an "open roof") by suturing the upper lateral cartilage with the septum at the cartilage part of the dorsum, can cause narrowing of the nose or even functional problems, breathing difficulty due to the narrowed nasal canal. Spreader grafts are used to solve these problems (Photo 4a, b, c, d). They are oblong-shaped cartilages usually 2-4 mm thick, 2-3 mm high and 15-20 mm long. They are placed between the septum and the upper lateral cartilages, sutured to these structures, providing a very good solution for both narrowed nasal dorsum and breathing difficulties through dilation of the nasal canal.

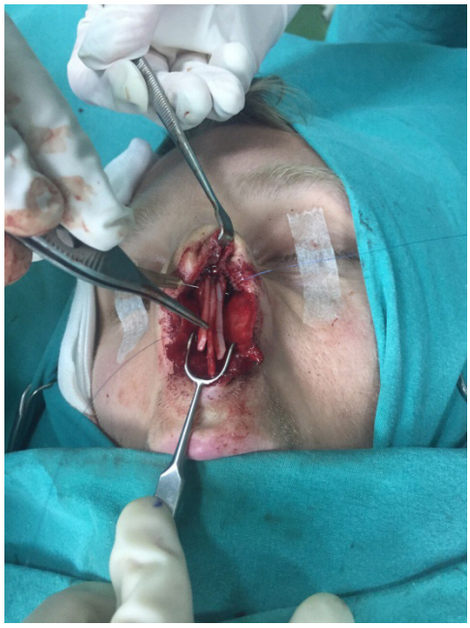


Photo 4a – spreader grafts on both sides of the nose.

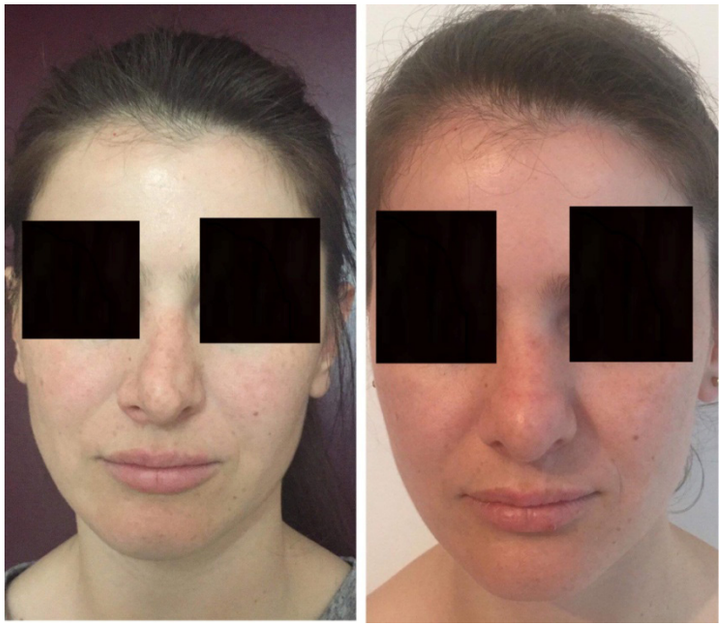


Photo 4b – female patient operated 8 years ago with closed rhinoplasty. The deformity is corrected with the use of spreader grafts.

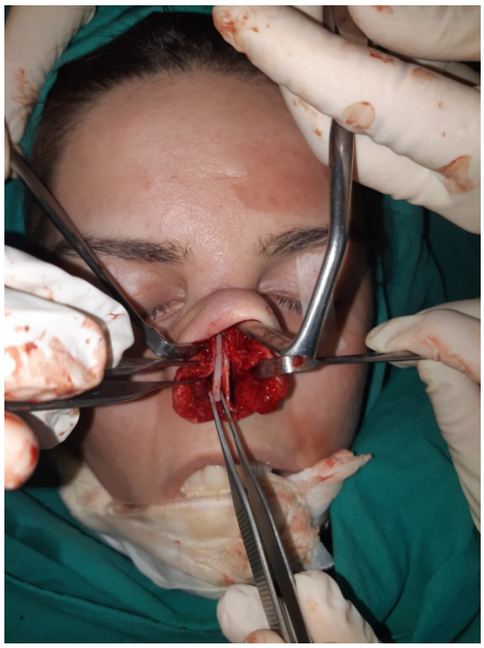
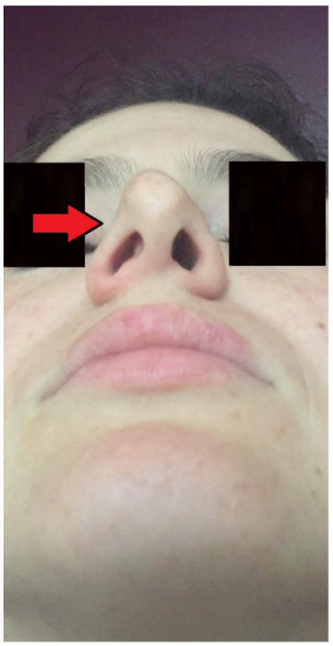


Photo 4c – one-sided spreader graft



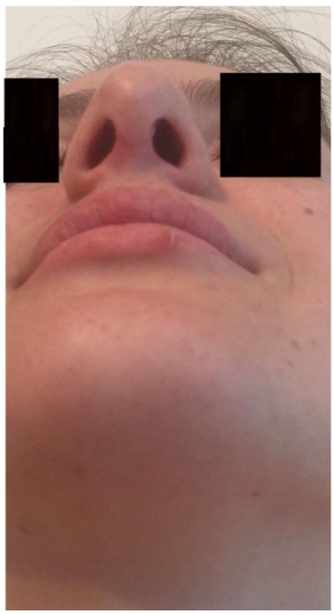
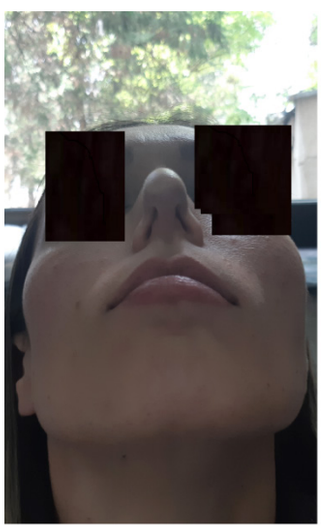


Photo 4d – Internal valve collapse on the right side after a previous closed rhinoplasty, combined with ipsilateral breathing difficulties. Both functional and esthetic problems are solved with the use of spreader graft.

Tip refinement grafts are thin, small grafts (usually less than 1 cm) that are often obtained from resected portions of lateral alar cartilage as soft structures or harvested from the conch of the ear. They can be designed in rectangular shape with rounded angles, shield, diamond, etc. They are used to refine the shape of the tip of the nose and are sewn to the dome, just to it or combined to the top of the medial crura.

Alar rim grafts are 2-3 mm x 10-15 mm longitudinal pieces of cartilage that are inserted into a small pocket, created by cutting from inside the mucous, several millimeters above the alar rim. The grafts can be placed directly without stitches into their pocket or stitched to the lower lateral cartilage. By strengthening the lower lateral cartilage and the external nasal valve, they provide a very simple yet practical solution for correction of the collapse of the alae nasi, which in turn causes obstruction of the nostrils and makes breathing difficult (Photo 5).



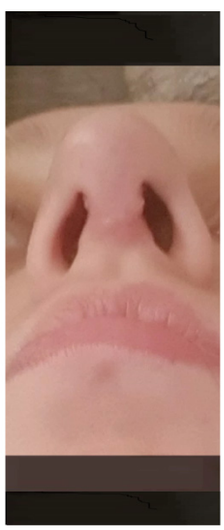


Photo 5 - Left: external valve insufficiency combined with breathing problems due to the closure of the nostrils. Right: the problem was corrected through application of alar rim grafts (photo two weeks after the surgery).

The last two decades have seen an increasing trend of utilizing diced cartilage grafts in rhinoplasty procedures, either as single or wrapped by fascia, especially as combined grafts for the correction of dorsal defects of the nose (Photo 6a, b, c, d, e, f, g, h). Diced cartilages have been shown to be both flexible and durable structures. These are cartilages harvested from one or more donor sites and cut into small 0.5 mm-sized pieces that shouldn't be compressed because they lose their viability. The fascial graft is harvested from the deep temporal fascia in required dimensions in a particular case and is then folded. Fascia is sewn on its free sides turning it into a small sack with only one open side as a sack orifice. The diced cartilage is first inserted into a syringe with a cut hub, and then by inserting the syringe into the fascia sac through the orifice it is filled with the diced cartilage as needed. The orifice is closed and the fascia filled with diced cartilage is inserted in its pocket under the skin to augment the defect of the dorsum. The graft is sutured in place with few stitches at the distal part while in the proximal part the fixation is done with a percutaneous suture at the level of the nasion. These grafts are soft, malleable, and when designed to the required size, they fit a great deal to the defect to be filled in, giving very good results, showing no prominences under the skin, especially in their sides, as is often the case with strong grafts.

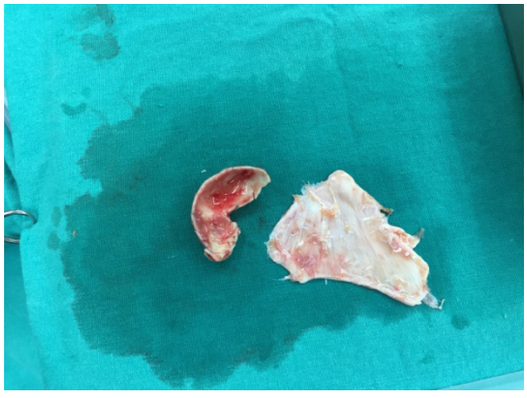
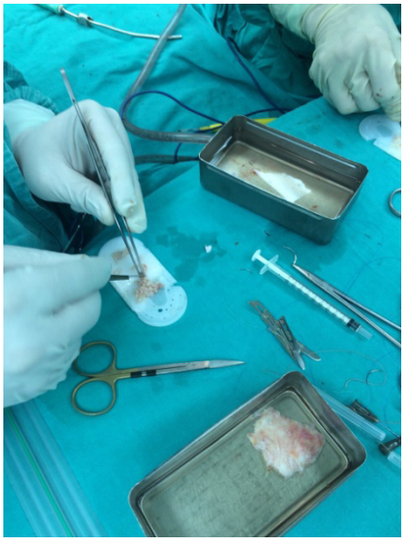
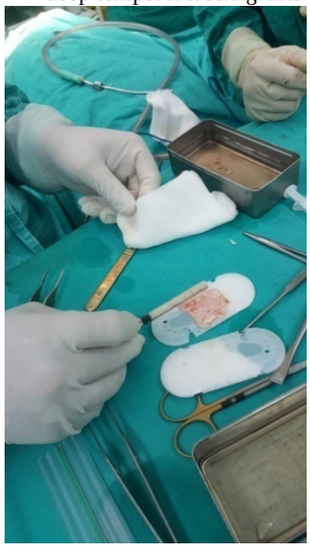


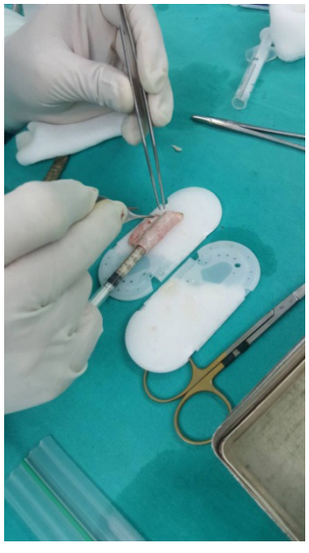
Photo 6a – harvested auricular concha and deep temporal fascia.grafts



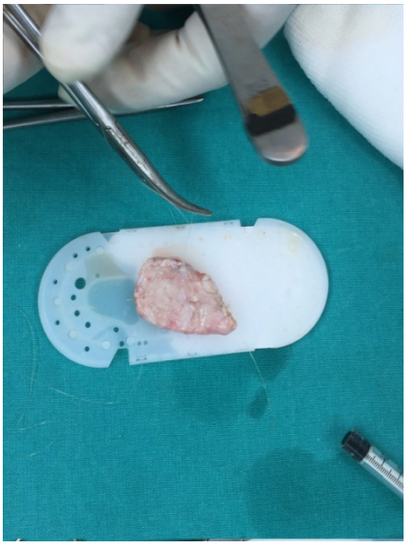
6b – cartilage cutting into small pieces



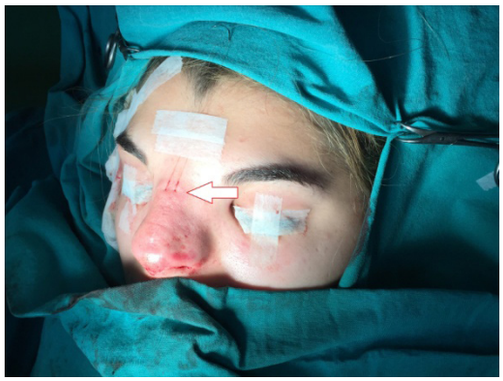
6c – the syringe is filled with diced cartilage grafts



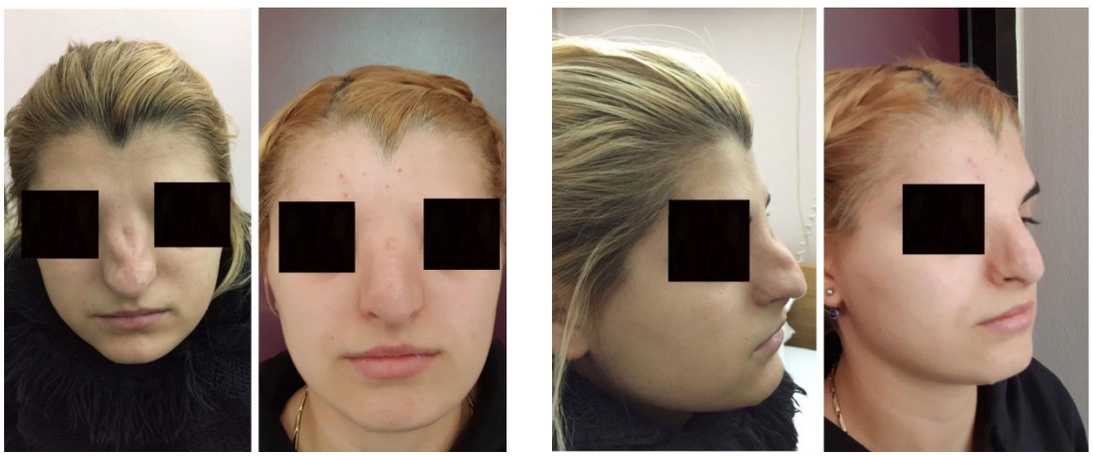
6d – suturing the fascia as a small sac and filling it with diced cartilage



6e –tying the orifice of the fascial sac after it has been filled with diced cartilage grafts



6f – percutaneus fixation of the fascia filled with diced cartilage after being inserted in the pocket under the dorsal skin



6g and 6h – female patient with hypertelorism and nose deformity, operated 6 years ago through an incision at the dorsum of the nose.

Frontal and side views, before and after the operation with the use of diced cartilage graft wrapped with deep temporal fascia.

Another way of using cartilage tissue, especially for filling small defects, is cutting the cartilage into very small parts and putting on them 1 or 2 drops of blood, which act as adhesive material (Photo 7a, b, c, d). This causes the particles to stick together and be taken as a single unit and placed in the small defects which they fill in by molding them easily. Cartilage as a strong structure is also used to augment the defects of the dorsum of the nose (Photo 9).

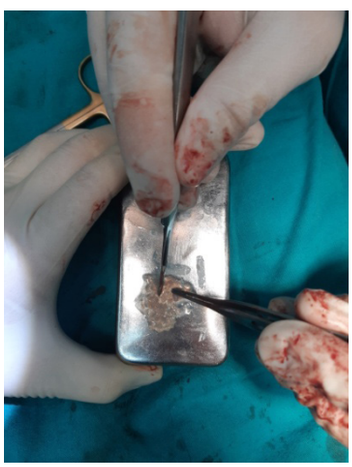
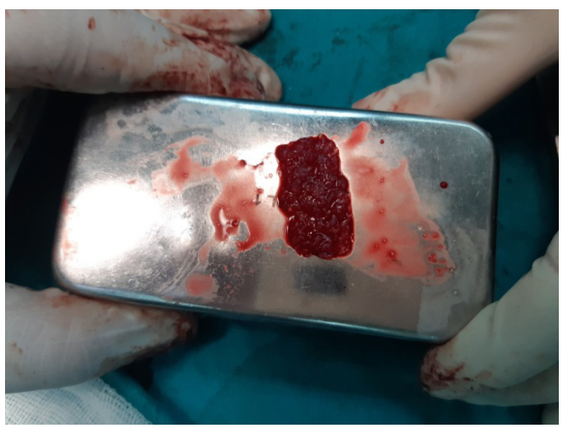
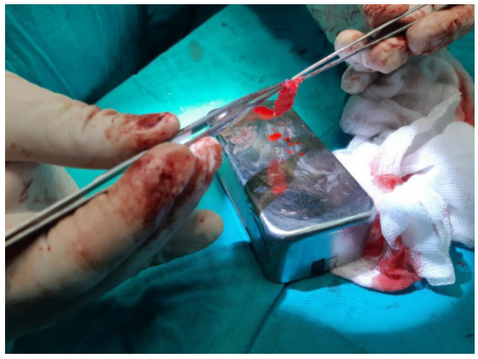


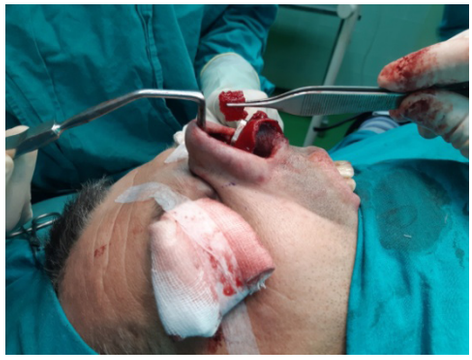
Photo 7a – cutting the cartilage into very small pieces



7b – cartilage pieces stuck with blood



7c – taking the graft as one unit



7d – application

Chondrocutaneous composite grafts which are usually harvested from the ear have shown good results in the correction of stenosis, which is often due to soft tissue fibrosis in the nasal vestibule as well as in the internal valve collapse. They are also used to correct distal deformities of the alae nasi, when the alar rim remains drawn upwards, and the composite graft is used for lowering alar rim several millimeters, bringing it into normal position.

Except for dorsal grafts, where the fascia can be used alone or in combination with diced cartilage, the fascia is also used to augment the nasal radix in cases where tissue depression in this area needs correction. In these cases the hollow of the root of the nose makes the prominence of the nasal tip more visible and indirectly radix augmentation with graft neutralizes the prominence of the nasal tip. In such cases the fascia, sewn with an absorbable suture, becomes a ball-shaped pile, which is then fixed through a percutaneous suture into its pocket at the root of the nose. Fascia also serves as a cover for hiding prominences of the nasal structures. This is particularly important to adjust in patients with thin skin nose where the visibility of different prominences is more pronounced (Photo 8).

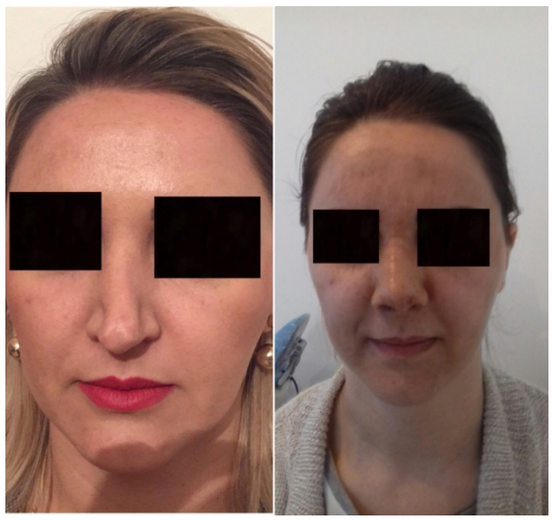


Photo 8 – female patient operated two years ago presenting with tip deformity of the nose, thin skin and visible cartilage prominences under the skin. Left: view before the operation. Right: view after the operation – plication of the lower lateral cartilages and coverage of nasal structures with deep temporal fascia graft.

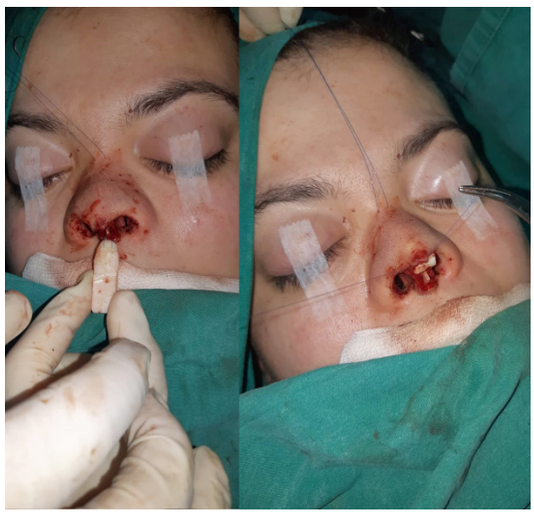


Photo 9 – rib graft for augmentation of dorsal deficiency of the nose

Bone as a graft, either alone or with cartilage (osteocartilaginous graft), is mainly used in rhinoplasty in the correction of dorsal defects of the nose, especially in cases with marked deficiencies of this part of the nose, better known as “saddle nose”.

Dermis is used as a graft in rhinoplasty in cases of nose deformities due to retraction of the nasal segments from the loss of the dermis.

CONCLUSION: Grafts have already become a common part of rhinoplasty operations. Many revisions and correction of complicated traumatic deformities nowadays are unthinkable without this procedure. Scientific literature is full of papers and case reports that confirm the usefulness of grafts both in open and closed rhinoplasty. The goal has always been to achieve long term results. The use of diced grafts, whether wrapped or not with fascia, has enriched the surgeons' creativity in finding impressive solutions to correct complex deformities. With a view of finding easier solutions to aesthetic and functional nasal problems, tempted also by the profit that it may bring, many firms are looking for other alternatives that would avoid difficult interventions requiring complex surgical procedures. In general, various prostheses produced so far have not shown satisfactory results. In their papers, prominent surgeons are skeptical about the use of fillers in the correction of aesthetic problems of the nose due to their short term effect, complications, and possible difficulties for a subsequent rhinoplasty. However, there are other surgeons who view fillers as an alternative for correcting isolated aesthetic problems and who have reported good results for several years. Whether industry and technology will succeed in replacing at least some of the cases of rhinoplasty with the use of grafts remains to be seen. Until then, grafts will certainly remain the golden standard to many complex problems.

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Profesional paper

THE CORRELATION BETWEEN CENTRAL CORNEAL THICKNESS AND AGE IN PATIENTS WITH REFRACTIVE ANOMALIES AND EMMETROP

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ABSTRACT

Purpose: The purpose of this study was to analyze mean central corneal thickness (CCT) and determine whether there are any correlations between CCT, age, and gender in the respondents with refractive anomalies and emmetropic.

Methods: This was a retrospective study that was conducted at the University Clinical Center of Kosovo, UCCK of the Republic of Kosovo, in a period of time from February 2016 to January 2018.The study was conducted in the Department of Ophthalmology and included a current group of 180 respondents with refractive anomalies, and 150 respondents with normal visual acuity (emmetropic).

Results: The mean CCT value was 552.2 μm SD=17, for all respondents with normal visual acuity. However, these values are statistically significant difference between ages, while according by gender in the hypertropy group, the CCT values were higher in women, where the average CCT was 569.1 μm (SD ± 28.9 μm), while in the group with myopia the CCT values were higher in men, with a CCT average 529.5 μm (SD ± 28.0 μm). Regarding the respondents with refractive anomalies it was found that in our study the mean value of the CCT in the hypermetropic group is 564.8 μm (SD ± 28.0 μm),for myopics 521.0 μm while in the astigmatic group the average value of CCT is 530.3 μm. According to the age group we got a difference with an important statistical significance between the groups (P<0,0001), cases with astigmatism were of the younger age group, compared to the group of Hypertropic (P<0,01) and Myopic (P<0,001). Results also revealed that in groups of patients with refractive anomalies, we did not found any significant relation between between average values of CCT by age group (P>0.05). While in the emmetropic group, with the increasing of the age, the values of CCT are reduced (P=0.003).

Conclusion: The standard value of central corneal thickness to respondents is differing according to the age and genders. The values of CCT decreased during the lifetime in the respondents with normal visual acuity. Also we found no statistically significant difference between gender and CCT (P>0.05) However, a statistically significant difference was found between men and women, in the hypertropy group where the CCT values was higher in women, and in the myopic group, CCT being higher in men. Also findings from this study, such as decreases in CCT values during the life, may assist us in the planning of refractory surgery, given the increasing tendency of such treatment of refractive anomalies.

Key words: central corneal thickness, visual acuity, pachymetry.

Introduction

The detection and management of contact lens related complications and certain surgical procedures (such as astigmatic keratectomy, LASIK) rely on the accurate measurement of CCT .Central corneal thickness (CCT) can be used to assess the corneal physiological condition as well as the pathological changes associated with ocular diseases. It has an influence on the measurement of intraocular pressure and is being used as a screening tool for refractive surgery candidates [1].

The cornea is part of the optical system of the eye, and its condition is directly related to the quality of eyesight [2][3]. The cornea is a transparent avascular tissue that acts as a structural barrier and protects the eye against infections [4]. Along with the tear film, it provides proper anterior refractive surface for the eye. Cornea contributes to two-third of the refractive power of the eye [5]. For a healthy cornea, the CCT has a very important role in glaucoma. Thin average CCT results in under estimation of the true Intraocular Pressure (IOP) and thicker average CCT results in over estimation of IOP [6]. Compared to emmetropic eye, myopic eye is longer and hyperopic eye is shorter [7]. Refractive errors are not preventable but can easily be treated with corrective eye glasses, contact lenses or in some cases, corrective surgery [8].

Corneal thickness is an important indicator of corneal health, and its alteration may be indicative of different pathologies [9]. Its measurement is the essential factor to assign to the corneal status, endothelial pump mechanism and in wide range of disorders; as ectatic dystrophies, contact lenses related complication, dry eye, and diabetes mellitus[10] [11]. Abnormally thick or thin measurements may indicate corneal anomalies. Pachymetry is an important procedure which needs to be measured prior to a LASER procedure to ensure sufficient corneal thickness is present, thereby preventing ectasias of the cornea. The measurements are essential, to decide on the setting of the baseline and the depth of the incision during the surgical procedure [12] [13]. Factors thought to affect CCT include race, age, sex, anthropometric parameters, drugs, time of day, blink rate, and type of measuring equipment used. It has also been established that CCT varies according to ethnicity. However, none of these factors alone is able to predict CCT [14] [15] [16].

Subjects and methods: Written informed consent was obtained from the respondents prior to the initiation of the study; possible risks were explained. The Declaration of Helsinki was adhered to in all procedures and the approval of the ethics committee of University of Pristina was obtained before the initiation of study. The confidentiality and anonymity of the surveyed respondents as well as their volunteer participation in the research have been respected. The respondents' data, documented, consists of gender, age and race. The study covered 330 respondents, in total 660 eyes, which on the basis of refractive anomalies are divided into four groups. In the Hypertropia group 65 respondents, Myopia 65, Astigmatism 50 and in the Control group were 150 or 45.5% of the respondents. According by gender and age, the present study was carried out on (330) resondents, divided into two groups. Group 1; included (180) respondents with refractive anomalies (118 males, 62 females) and group 2; included (150) respondents with normal visual acuity or emmetrop (94 males, 56 females). The respondents with normal visual acuity were chosen after a detailed history and visual exam. All respondents had healthy corneas. All had no previous ocular surgery, no ocular diseases or medication, and no history of contact lens wear .The participants in each group were divided according to their age into three subgroups; group a; from (<20) years, group b; from (20-29) years and group c; (above 30) years.

Study sample

The respondents who came to the clinic, as ambulatory cases with blurry vision symptoms, halos around bright lights, headaches, and haziness, were included in the group with refractive error, while the emmetropic group included respondents with 6/6 visual acuity, that did not have the abovementioned symptoms. The subjects were aged 18 to 40, from urban and rural areas. All respondents were of the same ethnic group.

Inclusion criteria

- Respondents with refractive anomalies who have not been diagnosed before;
- respondents with refractive anomalies between the age of 18 and 40 years old regardless gender;
- healthy volunteers
- respondents with necessity for refractive anomalies correction,
- normal corneal topography,
- IOP < 21 mmHg,
- Normal optic discs,
- Respondents who had no ocular disease,
- respondents who did not have eye surgery

interventions.

- respondents who have not previously had correction with glasses

Exclusion criteria

- Patients with glaucoma and previous corneal refractive surgery procedures;
- patients who have already been corrected for refractive anomalies;
- IOP >21 mmHg,
- evidence of other anterior segment pathology including corneal opacities,
- keratoconus,
- corneal oedema,
- presbyopic patients;
- patients with corneal lesions,
- with amblyopi,
- the respondents with stapheloma and retinal problems were excluded,
- the respondents with best visual acuity of 6/6 were excluded
- diabetes mellitus or other acute or chronic diseases possibly affecting the corneal thickness,
- any other optic nerve or intracranial disease
- no history of contact lens wear
- no ocular diseases or medication
- diseases associated with corneal pathology (rheumatoid arthritis)
- patients not willing to give consent.

Data Collection

Before the examinations the respondents were interviewed with standard questionnaire to obtain information of the adult's family history, study intensity, time spent doing outdoor activities and indoor activities, history of previous eye examinations and treatments, lifestyle, parental refractive anomalies, etc. Recorded data of respondents with an error of refraction were retrospectively collected for (360) eyes examined over a period of two years . The data collected thereafter were compared with those of normal eyes. After the informed consent was obtained, the respondents underwent a complete ophthalmic examination, including slit lamp examination, determination of visual acuity by Snellen chart, refractive anomalies by autorefractometer, optic axis length with ultrasound B scan, CCT measurement with pachymeter ultrasound, and undilated FOU examination with indirect ophthalmoscopy, biomicroscope.

Finally, all respondents underwent subjective refraction sciascopia, with Hydrochloride Cyclopentalate (1% drop). All measurements were performed in each eye individually. All measurements were made in the middle of the day, between 9:00 and 14:00 during a single visit. All ophthalmic imaging studies and non-ocular parameters documentation were taken after complete refraction tests. All respondents at the end of the research had the best corrected visual 6/6.

Statistical data analysis: The data processing was performed with the help of the statistical package SPSS 22.0 bn. The acquired data is presented in the tables and charts. The structure of the index, the arithmetic mean, the standard deviation, the minimal and maximal value have been calculated from the statistical parameters. The testing of the qualitative data was carried out with the help of the X 2 - test and Fisher's test, for the quantative data which had a normal distribution in the T – test. The correlation between the two phenomena was performed with Spearman's Correlation. The difference is significant if R.

Results

Table 1. Respondents by group and age-group

	Group								Total	
	Hypertropic		Myopic		Astigmatism		Control gr.			
	N	%	N	%	N	%	N	%	N	%
< 20	11	16.9	12	18.5	10	20.0	30	20.0	63	19.1
20-29	47	72.3	43	66.2	40	80.0	118	78.7	248	75.2
30+	7	10.8	10	15.4	-	-	2	1.3	19	5.8
Total	65	100.0	65	100.0	50	100.0	150	100.0	330	100.0

The majority of the surveyed respondents in the research from the four groups are at the age of 20-29 years with 75.2% (Table 1). The respondents included in the research were aged 18-40 years with an average age of 22.9 years (SD ± 4.0 years).

Table 2. The average age of the respondents by groups

Age (year)	Group				Total
	Hypertropic	Myopic	Astigmatism	Control gr.	
N	65	65	50	150	330
Average	23.8	24.2	21.6	22.3	22.9

SD	4.9	5.6	2.1	2.7	4.0
Min	18	18	18	18	18
Max	40	39	28	30	40
Kruskal Walis test	P=0.0001				

Dunn's Multiple Comparison test
Hypertropia vs. Myopia P>0.05 NS
Hypertropia vs. Astigmatism P<0.01 S
Hypertropia vs. Control P>0.05 NS
Myopia vs. Astigmatism P<0.001 S
Myopia vs. Control P>0.05 NS
Astigmatism vs. Control P>0.05 NS

According to the age group, we got a difference with an important statistical significance between the groups (P<0,0001) cases with astigmatism were of the youngest age group compared to the group of Hypertropia (P<0,01) and Myopia (P<0,001), (Table 2).

Table 3. Association of Age group with the type of refractive anomaly

Age - group (year)	Type of refractive error					
	Hypertropic		Myopic		Astigmatism	
	N	%	N	%	N	%
< 20	11	16.9	12	18.5	10	20.0
20-29	47	72.3	43	66.2	40	80.0
30+	7	10.8	10	15.4	-	-
Total	65	100.0	65	100.0	50	100.0
P-value	P=0.086					

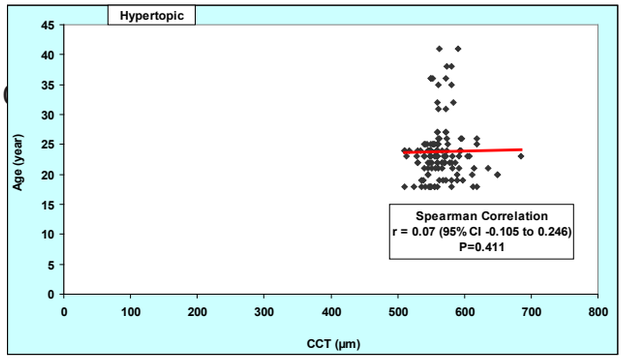
We did not find any significant relation between the age group and the refractive anomalies (P=0.086), (Table 3)

Table 4. Age - wise distribution of CCT by groups

Age (years)	N	Mean	SD	Min	Max	P-value
Hypertropic group						
<20	38	570.1	34.1	510	650	P=0.250
20-29	78	561.7	26.6	510	685	
30+	14	567.6	12.9	550	590	
Myopic group						
<20	40	520.6	41.0	420	618	P=0.200
20-29	70	517.4	34.5	438	573	
30+	20	534.3	41.0	461	590	
Astigmatism group						
<20	42	528.5	31.5	450	608	P=0.543
20-29	58	531.7	37.0	444	633	
Control group						
<20	106	557.6	19.7	517	611	P=0.003
20-29	190	549.5	15.7	472	595	
30+	4	545.5	4.0	542	549	

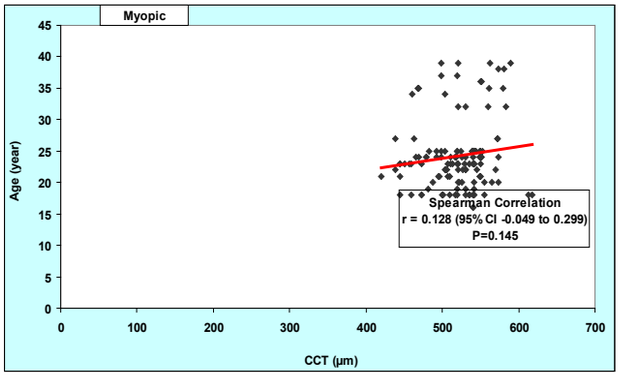
In groups of patients with refractive abnormalities, we have not found a difference with an important statistically significant difference between average values of CCT by age group (P>0.05).

In the Control group, with the increasing of the age, the values of CCT are reduced, in the age group below 20 years the average of CCT was 557.6 µm (SD ± 19.7 µm), in the age group 20-29 years the average of CCT was 549.5 µm (SD ± 15.7 µm), while in the 30+ years the average of CCT was 545.5 µm (SD ± 4.0 µm) difference with an important statistical significance (P=0.003), (Table 4).



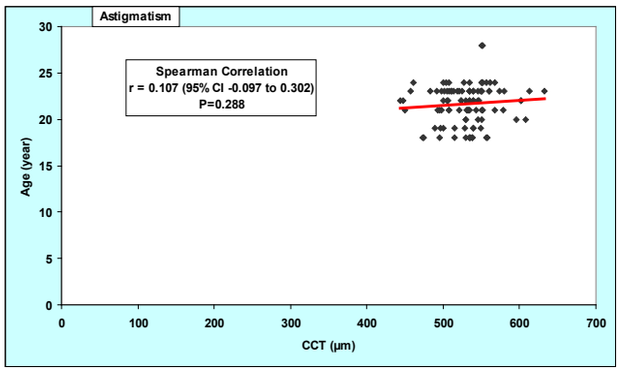
There was analyzed the degree of correlation between the values of CCT and the age in the group with hypertropy covered by the study. With the Spearman's correlation we did not find correlation (r = 0.07, 95% CI -0.105 to 0.246, p=0.495) between CCT and the age in the cases with hypertropy (Chart 1).

Chart 2. Correlation of CCT with Age at myopic



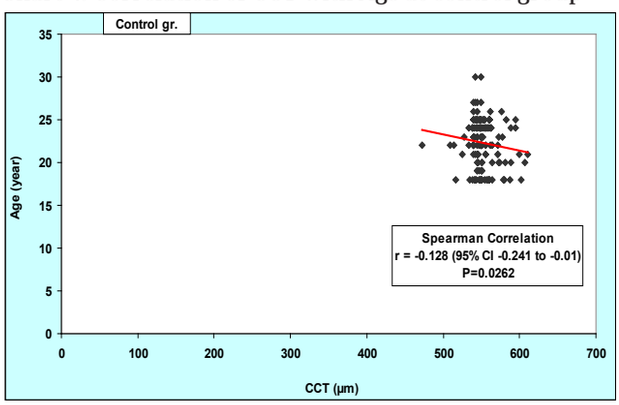
There was analyzed in the degree of correlation between the values of CCT and the age in the group with myopia covered by the research. With the Spearman's correlation an insignificant low-level correlation has been found (r = 0.128, 95% CI -0.049 to 0.299, p=0.145), (Chart 2).

Chart 3. Correlation of CCT with Age at astigmatism



There was analyzed in the degree of correlation between the values of CCT and the age in the group with Astigmatism covered by the research. With the Spearman's correlation an insignificant low-level correlation has been found (r = 0.107, 95% CI -0.097 to 0.302, p=0.288), (Chart 3).

Chart 4. Correlation of CCT with Age at control group



There was analyzed the degree of correlation between the values of CCT and the age in the control group covered by the research. With the Spearman's correlation a negative correlation was found, significant from a low degree (r = -0.128, 95% CI -0.241 to -0.01, p=0.0262), (Chart 4).

Table 5. Gender - wise distribution of CCT by groups

Gender	N(eyes)	Mean	SD	Min	Max	P-value
Hypertropic group						
F	90	569.1	28.9	510	685	P=0.013
M	40	555.1	23.5	510	618	
Myopic group						
F	82	516.0	41.8	420	618	P=0.049
M	48	529.5	28.0	461	581	
Astigmatism group						
F	64	527.3	33.3	444	633	P=0.346
M	36	535.8	36.7	461	608	
Control group						
F	188	551.7	19.6	472	611	P=0.124
M	112	553.3	13.5	528	602	

In the group of respondents with astigmatism and in the control group, we have not found a difference with an important statistical significance between average values of CCT in relation to gender (P>0.05). In the hypertropy group, the CCT values were higher in women where the average CCT was 569.1 µm (SD ± 28.9 µm) while in men the average of CCT was 555.1 µm (SD ± 23.5 µm) difference with a statistical significance (P=0.013). In the group with myopia, CCT values were higher in men with a CCT average 529.5 µm (SD ± 28.0 µm) while in women the average of CCT was 516.0 µm (SD ± 41.8 µm) difference with an important statistical significance (P=0.049). (Table 5).

Discussion

In our study, in emmetropic respondents the mean of values the CCT was 552.2µm SD=17.6. Regarding the respondents with refractive anomalies it was found that the mean value of the CCT in the hypermetropic group is 564.8 µm (SD ± 28.0 µm), for myopics 521.0 µm while in the astigmatic group the average value of CCT is 530.3 µm. The obtained CCT value, compared with the population of nearby countries, is the same that of the study of the Turkish population (552 µm) [17] and roughly the same in German population (554.2±34.8 µm) [18]. At the same time it should be taken in considering that all comparisons between the CCT studies are dependent on the standard population.

The largest number of those included in the study four groups was the age group 20-29 years with 75.2% (Table 1), given the fact that the total number of respondents in the

study was 18-40 years old.

Our study focused on a healthy respondent, with refractive errors in the above mentioned age group, because the period between these ages represents a refractive stability.

An important role presents the fact that the CCT values vary with age. The present study observes, that in the control group this value has decreased with age; the age group under 20 years of age CCT was 557.6 µm (SD ± 19.7 µm), age group 20-29 years the CCT average was 549.5 µm (SD ± 15.7 µm), whereas 30 years the CCT average was 545.5 µm (SD ± 4.0 µm), with statistical significance (P = 0.003), (Table 4).

In the present study it is found that thinner cornea was correlated with older age group. In group of patients with refractive anomalies we have not found a difference with a statistical significance between average values of CCT by age group (P>0.05).

This is reported to a large number of studies that the CCT decreases over the lifetime, meaning that older people have thinner CCT. According by Saulius Galgauskas, that older people have thinner corneas [19]. Kamiya et al examined 204 eyes from 204 healthy subjects, and reported that biomechanical data for the cornea change during the course of the lifetime, but could not identify significant changes in age-related CCT or intraocular pressure [20-22]. Mercieca et al reported that the cornea becomes thinner with age and mean CCT is lower in women than in men [23]. The impact of age on corneal thickness can explained in a number of different ways. Referring to theory based on histologic studies, the corneas of older people are thinner because of a reduction in keratocyte density and possible destruction of collagen fibers, and senior individuals are exposed to environmental factors for a longer period of time, which might influence corneal structure [24]. Hasemian et al demonstrated that corneal endothelial cell density decreases in persons until 60 years of age; however, the volume of these cells increases [25]. As yet there is no consensus among scientists as to whether the corneal endothelium and CCT are interdependent [26-27],

Also we found no statistically significant difference between gender and CCT (P>0.05) in the group of patients with astigmatism and in the control group. However, a statistically significant difference was found between men and women, in the hypertropy group where the CCT values was higher in women, where the average CCT was 569.1 µm (SD ± 28.9 µm), while in men the average of CCT was 555.1 µm (SD ± 23.5 µm) difference with an important statistical significance (P=0.013). In the myopic group ,CCT values were higher in men with a CCT average 529.5 µm (SD ± 28.0 µm) while in women the average of CCT was 516.0 µm (SD ± 41.8 µm) difference with an important statistical significance (P=0.049). (Table 5).

The study by Saulius Galgauskas has found no statistically significant difference between gender and CCT (P>0.05) [19]. But, a statistically significant difference was found between young men and women aged 18–29 years, with CCT being higher in men. Leskul et al did not find any correlation between these parameters in their study in Thailand, in which 467 subjects aged 12–60 years were examined [28]. Eballe et al examined 970 eyes in their study and reported finding no statistically significant difference in CCT between men and women [16]. Findings of other studies indicate that corneas are thicker in men than in women. Suzuki et al examined 2,848 men and 4,465 women and came to the same conclusion (finding a mean CCT of 521 µm in men and 514 µm in women) [29].

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Review

NDIKIMI I RREZIQEVE PROFESIONALE FIZIKE DHE KIMIKE NË PARAQITJENE E LËNDIMEVE NË PUNË

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REZYME

Hyrje. Lëndimet në punë paraqesin problem të rëndësishëm mjeksor, socal dhe ekonomik në mjedisin tonë.

Qëllimi. Qëllimi i hulumtimit është analiza e ndikimit të rreziqeve që vijnë nga faktorët fizik dhe kimik në paraqitjen e lëndimeve në punë.

Metodologjia. Është përcjellur paraqitja e lëndimeve në punë të dy grupeve të puntorëve. Grupin e eksponuar e përbëjnë 900 puntorë të cilët janë profesionalisht të ekspozuar ndaj dëmtuesve fizik dhe dëmtuesve kimik edhe atë mbi vlerën maksimale të lejuar. Grupin kontrollues e përbëjnë 300 puntorë të cilët nuk janë të ekspozuar ndaj këtyre rreziqve.

Rezultatet. Grupi i ekspozuar dhe kontrollues kanë qenë përafërsisht të strukturës së njejtë në lidhje me faktorët tjerë që ndikojnë në paraqitjen e lëndimeve. Në grupin e ekspozuar është regjistruar numër më i madh i puntorve me lëndime në punë se sa në grupin kontrollues. Në grupin e ekspozuar është vërejtur numër më i madh i puntorve me lëndime në vendin e tyre të punës dhe me lëndime gjatë rrugës që bëjnë prej shtëpije deri në punë dhe nga puna në shtëpi se sa në grupin kontrollues. Në nëngrupin e puntorve të grupit të ekspozuar të cilët rregullisht i shfrytëzojnë mjetet për mbrojtje personale është regjistruar numër më i vogël i puntorve me lëndime në punë në krahasim me numrin e puntorve me lëndime në punë të nëngrupit të puntorve të cilët nuk shfrytëzojnë rregullisht mjete për mbrojtje personale të cilat janë të nënshkruara me Aktin e caktimit të rrezikut për atë vend të punës.

Konkluzione. Faktorët dëmtues prezent në vendin e punës paraqesin faktorë të rëndësishëm që ndikojnë në paraqitjen e lëndimeve në punë, kurse shfrytëzimi i rregullt i mjeteve për mbrojtje personale paraqet masë të rëndësishme prventive.

Fjalë kyçe. Lëndimet në punë, dëmtimet fizike, ekspozimi profesional, dëmtimet kimike, mjetet mbrojtëse personale.

HYRJE

Pasojat e lëndimeve në punë dëmtojnë shëndetin e puntorëve dhe paraqesin një prej problemeve kryesor shëndetësor, ekonomik, social dhe prodhues të shoqërisë moderne (1-4). Përcjellja shumëvjeçare e shkaqeve të lëndimeve në punë përbën bazë të të dhënave për informim të parakohshëm të puntorit dhe punëdhënësit, përgaditje adekuate dhe promovim të shëndetit në punë, me çka mund të arrihet zvogëlim ose zbutje e pasojave.

QËLLIMI I PUNIMIT

Qëllimi i këtij hulumtimi është analiza e ndikimit të faktorëve dëmtues fizik dhe kimik në mjedisin e punës në paraqitjen e lëndimeve në punë.

METODOLOGJIA

Është përcjellur lëndimi në punë te dy grupe puntorësh. Në hulumtim u përfshinë 1200 punonjës të industrisë

ushqimore, tekstile, gomës, metalike dhe kimike. Janë matur vlerat e parametrave mikroklimatik, agensëve kimik, zhurmës, pluhurit dhe ndriçimit në vendin e tyre të punës. Grupën e ekspozuar e përbënin 900 puntorë të cilët ishin profesionalisht të ekspozuar nën ndikimin fizik (zhurma, mikroklima, ndriçimi) dhe dëmtusve kimik (agensëve kimik dhe pluhurit) mbi vlerën maksimale të lejuar. Grupën kontrolluese e përbënin 300 puntorë të cilët nuk kanë qenë të ekspozuar ndaj këtyre rreziqeve. U morën anamneza personale, të dhëna për shfrytëzimin e rregullt të mjeteve mbrojtëse personale të parapara me Aktin e vlerësimit të rrezikut, u bënë kontrolla klinike dhe duke shikuar në kartelën shëndetësore në ordinancën e mjekut të zgjedhur familjar janë analizuar sëmundjet dhe lëndimet nga të cilat janë goditur puntorët gjatë vitit të fundit. Burim i të dhënave për analizë të lëndimeve në punë kanë qenë të dhënat e mbushura për paraqitje të lëndimeve në punë. Dallimi i vlerës statistikore të parametrave të hulumtuar ndërmjet grupit të ekspozuar dhe kontrollues është llogaritur me përdorimin e hi kuadratit dhe T-testi i Studentëve.

REZULTATET

Puntorët e grupit të ekspozuar janë nën ndikim të vlerave me rëndësi statistikore më të ulëta të temperaturëes së ajrit në mjedisin e punës në perioden dimërore, në raport me puntorët e grupit kontrollues. Puntorët e grupit të ekspozuar ishin nën ndikim të vlerave me rendësi statistikore më të larta të temperaturës së ajrit në ambientin e punës në periudhën verore, vlerave më të larta të lagështisë relative të ajrit dhe vlerave më të larta të shpejtësisë së rrymimit të ajrit në raport me puntorëte grupit kontrollues.Vlerat e matura të parametrave kimik të puntorve të grupit të ekspozuar ishin mbi vlerën maksimale të lejuar dhe me rendësi statistikore më të madhe në krahasim me vlerat e matura në vendin e punës së puntorve të grupit kontrollues. Niveli i zhurmës së matur në vendin e punës së puntorve të grupit të ekspozuar është me rëndësi statistikor më të lartë në krahasim me nivelin e zhurmës së matur në vendin e punës së puntorve të grupit kontrollues . Pluhuri në vendin e punës së puntorve të grupit të ekspozuar është present me vlerë më të lartë me rëndësi statistikore në krahasim me koncentrimin e pluhurit në ajër në vendin e punës së puntorve të grupit kontrollues. Ndriçimi në vendin e punës së puntorve të grupit të ekspozuar ka qenë me rëndësi statistikore më të ulët në raport me vlerat e matura të ndriçimit të vendit të punës së grupit kontrollues (Tabela nr.1).

Në mes grupeve të ekspozuara dhe kontrolluese të puntorve nuk egzistonte ndonjë ndryshim me rëndesi statistikore në prezencen e faktorëve të cilët mund të ndikojnë në paraqitjen e lëndimeve në punë (mosha, përvoja e punës, arsimimi, gjendja martesore, të ushqyerit, pirja e duhanit, konsumimi i alkoolit, puna në ndërrime, puna sipas normës, ndërrimi i natës, prezenca e sëmundjeve). Në grupin e ekspozuar me rëndësi statistikore është regjistruar numër më i madh i puntorëve me lëndime në punë se sa te grupi kontrollues. Te grupi i ekspozuar është vërejtur me rëndësi statistikore numër më i madh i puntorëve me lëndime në vetë vendin e punës dhe me lëndime në rrugën që kalojnë nga shtëpija në punë dhe nga puna në shtëpi, se sa te grupi kontrollues (Tabela nr.2). Te grupi i ekspozuar në raport me madhësinë e lëndimeve, është regjistruar me rëndësi staistikore numër më i mdh i puntorëve me lëndime më të lehta në raport me atë kontrollues, por nuk është vërtetuar ndonjë dallim me rëndësi statistikore në numrin e puntorëve me lëndime të rënda, lëndimeve të rrezikshme për jetën dhe lëndimeve vdekjeprurëse ndërmjet këryre dy grupeve (Tabela nr.3). Në nëngrupin e grupit të puntorve të ekspozuar që rregullisht shfrytëzojnë mjete për mbrojte personale është regjistruar me rëndësi statistikore numër më i vogël i puntorve me lëndime në punë në krahasim me numrin e puntorve me lëndime në punë të nëngrupit të puntorve të cilët nuk shfryzëzojnë mjete për mbrojtje personale (Tabela nr.4)..

DISKUTIMI

Të shumtë janë faktorët që ndikojnë në paraqitjen e lëndimeve në punë, ku më i rëndësishëm është faktori njeri dhe karakteristikat e tij siç janë: mosha, përvoja e punës, gjinia, adaptimi në vendin e punës dhe ambientit të ri, nevoja për përmbushjen e normës si dhe afirmimi personal në vendin e ri të punës, arsimimi, gjendja martesore, të ushqyerit, pirja e duhanit dhe konsumimi i alkoolit, gjendja psikofizike e puntorit dhe prezenca e sëmundjeve (5-11). Të dhënat nga literatura tregojnë se të rinjtë dhe ato punëtorë pa përvojë më shpesh lëndohen në vendin e punës (12), kurse në vendet në tranzicion më shpesh lëndohen punëtorët më të vjetër, të cilët kanë mbetur pa vende të punës, dhe duke dashur që të fitojnë për jetesë punësohen në vende të punës për ku nuk kanë përvojë dhe arsim të mjaftueshëm(13).

Në këtë hulumtim nuk kishte ndonjë dallim të rëndësishëm statistikor në prezencën e fakteve në lidhje me faktorin

njeri te punëtorët e grupit kontrollues dhe të ekspozuar. Nuk kishte as ndryshim të rëndësishëm statistikor në lidhje me kërkesat e punës (puna në ndërrime, puna sipas normës, puna gjatë natës) ndërmjet këtyre dy grupeve të hulumtuara. I vetmi ndryshim ndërmjet këtyre dy grupeve të punëtorëve ishte në prezencën e faktorëve dëmtues fizik dhe kimik në ambientin jetësor dhe punues te të hulumtuarit e grupit të ekspozuar. Te grupi i ekspozuar është regjistruar me rëndësi statistikore numër më i madh i punëtorëve që kanë pasur lëndime në vendin e punës dhe në udhëtimin prej shtëpije në punë dhe prej pune në shtëpi në krahasim me grupin kontrollues. Prezencë të tillë të lartë signifikante të lëndimeve në punë te punëtorët e grupit të eksponuar tregohet me prezencën e faktorëve dëmtues në ambientin jetësor dhe punues të këtyre punëtorve të hulumtuar. Këto hulumtime janë në përputhëshmëri me rezultatet që në literaturë i gjejmë te autorë të tjerë(14-16). Faktorët jo të përshtatshëm mikroklimatik posaçërisht lagështia dhe temperatura jo adekuate e ajrit, mund të ndikojnë negativisht në mënyrë direkte në gjendjen psikofizike të punëtorëve dhe të sjellin deri te paraqitja e lëndimeve. Faktorët joadekuat mikroklimatik pengojnë qarkullimin, sjellin deri te paraqitja e lodhjes që paraqet faktor që predisponon paraqitjen e lëndimeve në punë (17). Ndriçimi joadekuat është shpesh shkaktar i lëndimeve dhe është i rëndësishëm jo vetëm zvogëlimi i ndriçimit por dhe drita e padurueshme si dhe ajo veptuese (18). Zhurma është faktor i rëndësishëm që shkakton lodhje të punëtorëve dhe gjatë punës e rëndon dhe e pengon komunikimin gojor dhe vërejtjet e dhëna dhe në këtë mënyrë sjell deri te lëndimet në punë . Në literaturë ka paraqitje pozitive të korelacionit ndërmjet nivelit të zhurmës në punë dhe praraqitjes së lëndimeve në punë (19). Avulli dhe gazrat mund të sjellin deri te lëndimet, nëse bëhet fjalë për materiale ndezëse dhe eksplozuese. Aerosolet dhe pluhuri zvogëlojnë të pamurit (20), që e rrit rrezikun për paraqitjen e lëndimeve. Posaqërisht rëndësi të madhe i takon monoksidit të karbonit i cili sjell deri te hipoksia e sistemit nervor qëndror, që ka si pasojë zvogëlim të koordinimit të lëvizjeve, paraqitje të shpejtë të lodhjes, ngadalësim të psikomotorikës, pra e zmadhon paraqitjen e lëndimeve në punë (21). Dëmtues tjerë në ambientin e punës së punëtorëve të grupit të ekspozuar, të detektuara në këtë hulumtim si dioksidi i sulfurit, acidi sulfurik, oksidi i zinkut, sulfati i bakrit, sulfati i magnezit, ksiloli dhe klori, shkaktojnë ndryshim në sistemin nervor të punëtorëve, dhe ashtu në mënyrë indirekte mundësojnë paraqitjen e lëndimeve në punë (22). Me rëndësi të veçantë është se u vërejtë që përdorimi i mjeteve mbrojtëse personale në punë shumëfish zvogëlon rrezikun nga paraqitja e lëndimeve në punë. Kjo është në pajtueshmëri me hulumtimin e autorëve të tjerë që kanë treguar se përdorimi i tyre shumë herë (rëndësishëm) zvogëlon rrezikun nga lëndimet, madhësinë e lëndimeve dhe numrin e ditëve të pushimit mjekësor për shkak të lëndimeve në punë (23).

KONKLUZIONI

Dëmtuesit fizik dhe kimik në vendin e punës paraqesin faktorë që kanë ndikim të madh në paraqitjen e lëndimeve në punë te punëtorët e ekspozuar. Përdorimi i rregullt i mjeteve për mbrojtje personale paraqesin faktorë të rëndësishëm në parandalimin e tyre.

SHTOJCA

Tabela nr. 1. Reziqet profesionale në vendin e punës së puntorve të grupit të ekspozuar dhe kontrollues

Rreziqet profesionale-llojet		Grupi i ekspozuar N=900	Grupi kontrollues N=300	t	p
Parametrat mikroklimatik	Temperatura e ajrit – Periudha dimrore(0C)	10.2 ± 1.1	19.2 ± 1.8	103,03	<0,0001
	Temperatura e ajrit – Periudha verore(0C)	30.2 ± 2.1	21.2 ± 1.7	67,24	<0,0001
	Lagështija relative e ajrit (%)	67.4 ± 11.7	48.3 ± 5.4	27,31	<0,0001
	Shpejtësia e rrymimit të ajrit (m/s)	0.9 ± 0.2	0.2 ± 0.003	60,6	<0,0001
Nokset kimike	Monoksidi i karbonit (mg/m3)	68.4 ± 9.4	38.1 ± 1.7	55,51	<0,0001
	Acidi sulfurik (mg/m3)	1.9 ± 0.8	0.01 ± 0.003	40,91	<0,0001
	Dioksidi i sulfurit (mg/m3)	8.7 ± 1.2	1.3 ± 0.09	106,68	<0,0001
	Oksidi i zinkut (mg/m3)	12.5 ± 1.4	0.2 ± 0.01	152,13	<0,0001
	Sulfati i bakrit (mg/m3)	2.3 ± 0.5	0.1 ± 0.02	76,17	<0,0001
	Sulfati i magnezit (mg/m3)	8.7 ± 0.3	1.1 ± 0.01	438,58	<0,0001
	Ksiloli (mg/m3)	483.8 ± 12.1	25.2 ± 3.4	647,98	<0,0001
	Klori (mg/m3)	9.8 ± 0.5	1.2 ± 0.07	124,03	<0,0001
Zhurma(dB)		103.8 ± 12.7	59.1 ± 5.2	51,13	<0,0001
Pluhuri (mg/m3)		19.8 ± 3.2	1.3 ± 0.9	98,18	<0,0001
Ndricimi (Lux)		64.2 ± 3.4	104.8 ± 4.9	159,1	<0,0001

Tabela nr. 2 . Lëndimet në punë te puntorët e grupit te ekspozuar dhe atij kontrollues

Lëndimet në punë	Grupi i ekspozuar N = 900		Grupi kontrollues N = 300		Hi kuadrat test	p
	Nr.	%	Nr.	%		
Lëndimet në vendin e punës	149	16,55	3	1	47.82	<0,01
Lëndimet gjatë rrugës prej shtëpije në punë dhe prej pune në shtëpi	74	8,22	1	0,33	22.57	<0,01
Gjithesej	223	24,77	4	1,33	79.11	<0,001

Tabela nr. 3. Lëndimet te puntorët e grupit te ekspozuar dhe atij kontrollues sipas rëndësisë

Kualifikim i lëndimeve	Grupi i ekspozuar			Grupi kontrollues			Hi kuadrat test	p
	N	nr	%	N	nr	%		
I lehtë	900	208	93,27	300	2	50	71.81	<0,001
I rëndë	900	11	4,93	300	1	25	1.01	n.s.
I rrezikshëm për jetë, vdekjeprus	900	4	1,97	300	1	25	0.06	n.s.
Gjithesej	900	223	100	300	4	100	79.01	<0,001

n.s.- ndryshimi nuk eshte statistikisht signifikant

Tabela nr. 4. Lëndimet sipas rëndësisë te puntorët e grupit te ekspozuar në raport me mbajtjen rregullisht të mjeteve për mbrojtje personale

Kualifikimi lëndimeve	Rregullisht shfrytëzojnë mjete mbrojtëse personale			Nuk shfrytëzojnë rregullisht mjete mbrojtëse personale			Hi kuadrat test	p
	N	nr	%	N	nr	%		
I lehtë	418	12	2,87	482	196	40,66	177.81	<0,0001
I rendë	418	3	0,72	482	8	1,66	0.95	n.s.
I rrezikshëm për jetën dhe vdekjeprus	418	1	0,23	482	3	0,62	0.13	n.s.
Gjithsej	418	16	3,83	482	207	42,95	181.7	<0,0001

n.s.- ndryshimi nuk eshte statistikisht signifikant

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Review

KARAKTERISTIKAT ANATOMIKE TË DEGËVE PERFORANTE TË SEGMENTIT A1 TË ARTERIES SË PËRPARME TRUNORE

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ABSTRAKT

Hyrje. Arteria e përparme trurore, arteria cerebri anterior (ACA), është zakonisht degë më e hollë mediale e ACI. Segmenti fillestar i ACA shtrihet medialisht nga trigonum olfactorium, dorzalisht nga n. opticus dhe chiasma opticum, ventralisht dhe rostralisht nga hipotalamusi, në cisterna laminae terminalis. ACA jep numrin më të madh të degëve leptomeningeale për vaskularizimin e faqeve mediale të hemisferave të trurit të madh. Segmenti proksimal A1 i ACA shtrihet prej vendit të fillimit të ACI deri te vendi i krijimit të AcomA. Arteriae perforantes të cilat ndahen nga segmenti A1, janë të pranishme gjithmonë, përbëhen nga 1-12 arterie. Numri i degëve varet nga zhvillimi i arteries së Heubner-it. Këto degë gjithmonë ndahen nga faqja dorzale e segmentit A1, deri në vendin e depërtimit në substantia perforata anterior. Vendi i depërtimit është zakonisht medialisht nga AL, ndërsa rostralisht nga degët e ACI dhe AChA. Të gjithë degët perforante ndahen në degë të vogla, prej 80-200 μm , mesatarisht 122 μm dhe të mëdha 210-710 , mesatarisht 325 μm.

Përfundim. Okluzioni i segmentit A1 të ACA jep më pak deficite neurologjike për shkak të ekzistimit të AcomA dhe qarkullimit kolateral nga ana e kundërt.

Fjalë kyçe: arteria e përparme trunore, degët perforante, segmenti A1

HYRJE

Arteria e përparme trurore, arteria cerebri anterior (ACA), është zakonisht degë më e hollë mediale e ACI. Segmenti fillestar i ACA shtrihet medialisht nga trigonum olfactorium, dorzalisht nga n. opticus dhe chiasma opticum, ventralisht dhe rostralisht nga hipotalamusi, në cisterna laminae terminalis. Trungjet e ACA të djathtë dhe të majtë janë të drejtuara rostralisht dhe medialisht, kah fisura interhemisferike, ku u bashkohet trungu i AcomA. Në vazhdim ACA kalon siperfaqësisht faqen mediale të hemisferës, më së pari ventralisht dhe rostralisht nga corpus callosum, dhe pastaj dorzalisht nga këto struktura. Zakonisht ndahet në dy degë përfundimtare: a. pericllosa dhe a. callosomarginalis, ndërsa përshkruhen këto degë kortikale kolaterale të cilat i marrin emrat varësisht prej fushës morfologjike të cilën e vaskularizojnë: a. frontobasalis, a. polaris frontalis, a. frontalis anteromedialis, a. frontalis intermediomedialis, a. frontalis posteromedialis, a. paracentralis, aa.

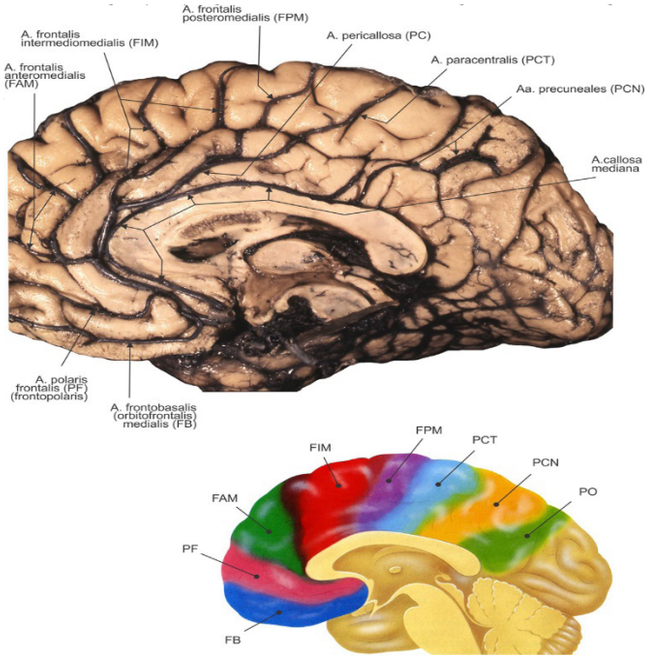

Figura 1. Degët kortikale të ACA (S. Bexheti me bashkëpunëtor: "Atlas i diseksionit të njeriut").

ACA jep numrin më të madh të degëve leptomeningeale për vaskularizimin e faqeve mediale të hemisferave të trurit të madh (Figura 1). ACM, pas kalimit nëpër zonën insulo-operkulare (Figura 2), vaskularizon kryesisht faqen superolaterale të hemisferës. AChA furnizon me gjak, ndër të tjera, edhe pjesën ventralo-rostrale të korteksit limbik. ACP e vaskularizon mezencefalonin, pjesën më të madhe të diencefalonit dhe faqen kaudale të hemisferave (3). AB vaskularizon ponsin, ndërsa AV palcën e zgjatur dhe palcën kurrizore (Figura 3). Këto enë të mëdha të gjakut janë të paraqitura edhe në preparatin e përbashkët (Figura 3).

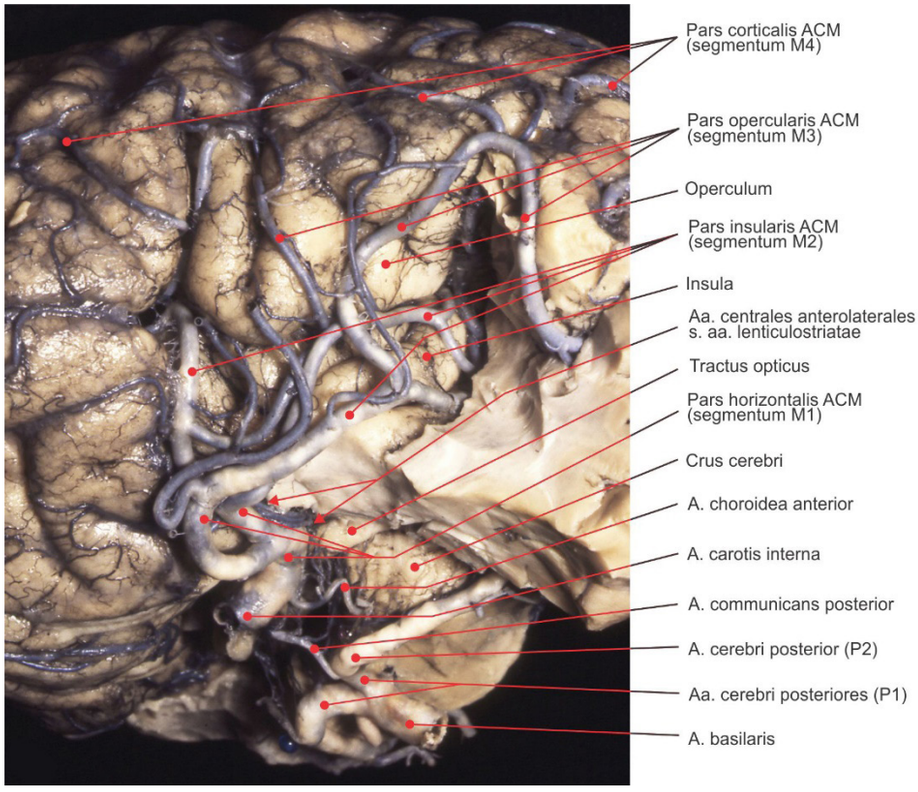

Figura 2. Rruga dhe degëzimi i ACM të majtë (S. Bexheti me bashkëpuntorë: „Atlas i diseksionit të njeriut").

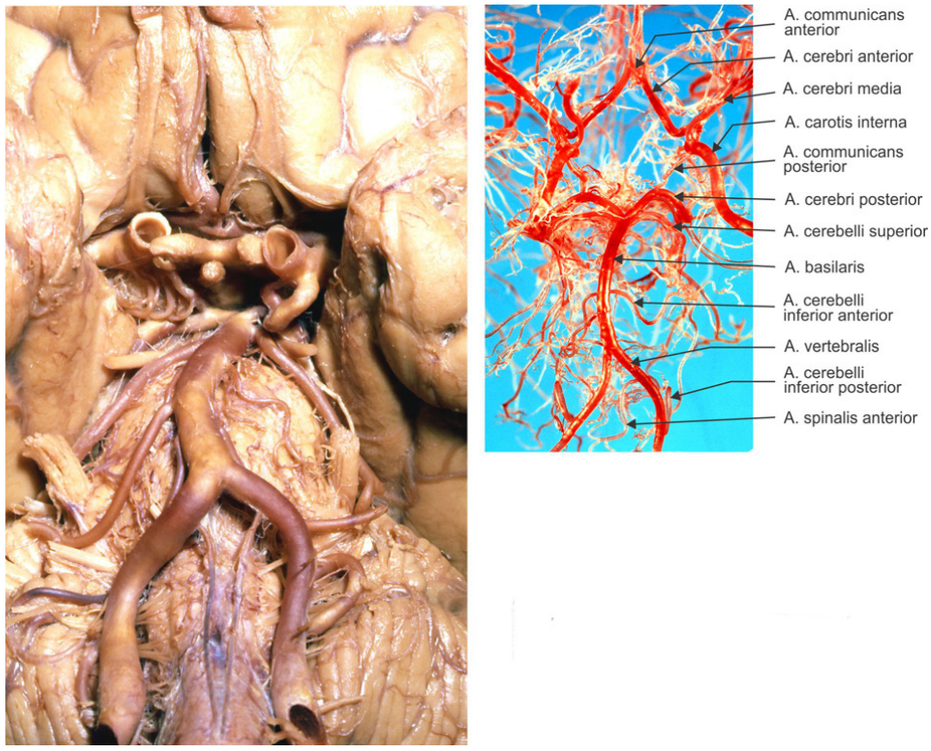

Figura 3. Preparat i arterieve të bazës së trurit, preparate me formalinë dhe korozive nga libri S. Bexheti me bashkëpuntor: „Atlas i diseksionit të njeriut“.

Karakteristikat morfologjike të segmentit A1 të ACA

Segmenti proksimal A1 i ACA shtrihet prej vendit të fillimit të ACI deri te vendi i krijimit të AcomA (Figura 4). Sipas përshkrimeve, segmenti A1 në 70% të rasteve shtrihet dorzalisht nga hiazma optike dhe zakonisht është në kontakt me të (4). Ndërsa në 30% tjera A1 është i drejtuar rostralisht dhe dorzalisht nga nervi optik, shumë rrallë ventralisht nga ajo, ku ndahet më herët dhe nën ACI, menjëherë pas fillimit të arteries oftalmike.

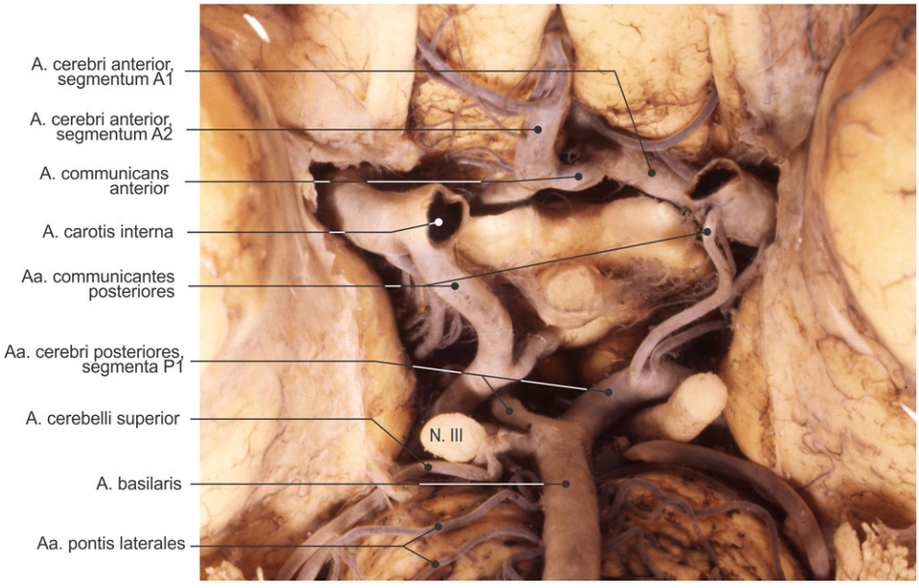

Figura 4. Preparat i arterieve të rrethit të Willisit në bazën e trurit të injektuara me tush dhe xhelatinë, preparat nga libri i S. Bexheti dhe bashkëpuntor: „Atlas i diseksionit të njeriut“.

Forma e segmentit A1 është e ndryshme, më së shpeshti në formë të shkronjës S (52,5%), më rrallë në formë harkore (32,5%), dhe mjaft rrallë e përdredhur (15%). Janë të shumta studimet radiologjike për formën e këtij segmenti. Është interesant fakti se, në moshë mesatare, ky segment ka drejtim horizontal të shtrirjes (20,1%), pastaj në formë të harkut konkav dorzalisht (30%) ose ventralisht (19,1%), ose pozitë të pjerrtë ventralisht (20,1%) ose dorzalisht (2,8%), si dhe në formë rrethore (8%) (që na kujton në fenestrim) (5, 6). Diametri i segmentit A1 në literaturë sillet prej 0,3 deri në 5,0 mm, mesatarisht 2,0-2,6 mm, ndërsa gjatësia 7,2-23,6 mm, mesatarisht 12,7-15 mm (7, 8). Hipoplazioni i segmentit A1 është dukuri e shpeshtë dhe përshkruhet si hipoplazion i lehtë, e cila ekziston në 14% të hemisferave dhe hipoplazion i shprehur në 8% të rasteve (8). Fenestrimi i A1 gjithashtu paraqitet shpesh, në 4,8% deri në 9,1% të rasteve (9). Duplikacioni i segmentit A1 është fenomen i rrallë i cili paraqitet në mënyrë sporadike (10) (Figura 5, 6).

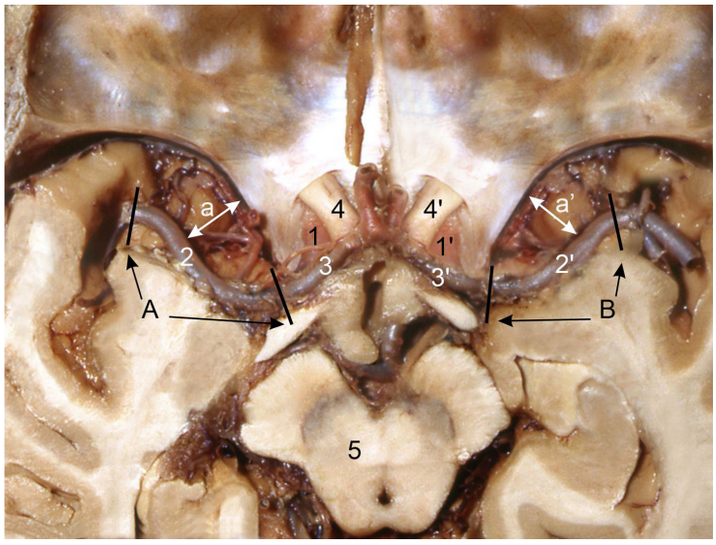

Figura 5. Shikim i faqes së brendshme të bazës së kafkës. Është i larguar lobus frontalis, prerje transversale nëpër lobus temporalis dhe mesencephalon. ACI (1, 1') e djathtë dhe e majtë japin ACM (2, 2') të djathtë dhe të majtë dhe ACA të djathtë dhe të majtë (3, 3'), n. opticus (4, 4'), mesencephalon (5).

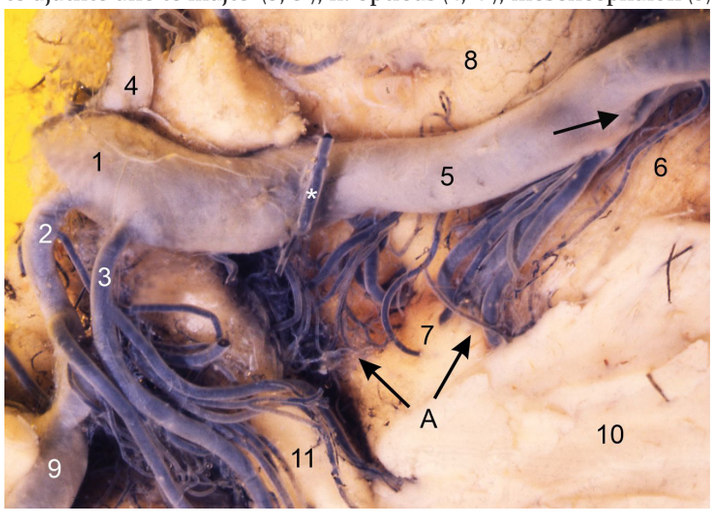

Figura 6. ACI e majtë (1) jep ACoP (2), AChA (3), ACA (4) dhe segmentin M1 ACM (5), i cili përfundon në nivel të limen insulae (6). Substantia perforata anterior (7), gyri orbitales (8), ACP (9), lobus temporalis (i larguar) (10), tractus opticus (11), aa. lenticulostriatae (A), a. temporalis polaris (*), shikim nga poshtë i hemisferës së majtë.

Ndarja e zakonshme e degëve të arterieve kryesore të trurit është në leptomeningeale, perforante dhe horoidale.

Degët perforante të segmentit A1 të ACA (aa. centrales anteromediales)

Arteriae perforantes të cilat ndahen nga segmenti A1, janë të pranishme gjithmonë, përbëhen nga 1-12 arterie, mesatarisht 6,6 në hemisferë (11). Numri i degëve varet nga zhvillimi i arteries së Heubner-it. Këto degë gjithmonë ndahen nga faqja dorzale e segmentit A1, deri në vendin e depërtimit në substantia perforata anterior. Shumica e degëve degëzohen përpara depërtimit në indin truror, ashtu që në nivel të vendit të depërtimit numri i tyre rritet. Vendi i depërtimit është zakonisht medialisht nga AL, ndërsa rostralisht nga degët e ACI dhe AChA. Të gjithë degët perforante ndahen në degë të vogla, prej 80-200 μm , mesatarisht 122 μm dhe të mëdha 210-710 , mesatarisht 325 μm. Degët e mëdha perforante dalin nga segmenti A1 në afërsi të degëzimit të ACI (12, 13, 14). Degët e vogla dhe të mëdha perforante vaskularizojnë commissura anterior, pjesën mediale të globus pallidus, një pjesë të crus anterius capsulae internae dhe pjesën ventromediale të caput nuclei caudati.

Arteria striata medialis longa s. recurrens Heubner, arteria e Hojbnerit, është trung i veçantë i përbashkët i arterieve perforante. Është gjithmonë i pranishëm, përveç në rastet ekstreme të hipoplazionit të segmentit A1 (15). Më së shpeshti ekziston një arterie, më rrallë dy (2-12%). Ndahet nga faqja dorzolaterale e ACA, në afërsi të bashkimit me AcomA në 8-35%, nga segmenti A1 në 8-14%, ose distalisht nga bashkimi me AcomA në 35-78% të hemisferace (16). Pas krijimit të saj, arteria Hojbner ka rrugë kthyese, e drejtuar kaudalisht dhe lateralisht. Më së shpeshti në indin truror depërton në pjesën laterale të substantia perforata anterior, menjëherë rostralisht nga AL. Kalibri i saj është prej 0,2-2,9 mm, mesatarisht 0,9 mm. Gjatësia e arteries është nga 12 deri në 38 mm, mesatarisht 23,4 mm (17). Arteria e Hojbnerit me degët e saja intracerebrale vaskularizon pjesën rostrale të caput nuclei caudati dhe pjesën fqinje të crus anterius capsulae internae (18) (Figura 7).

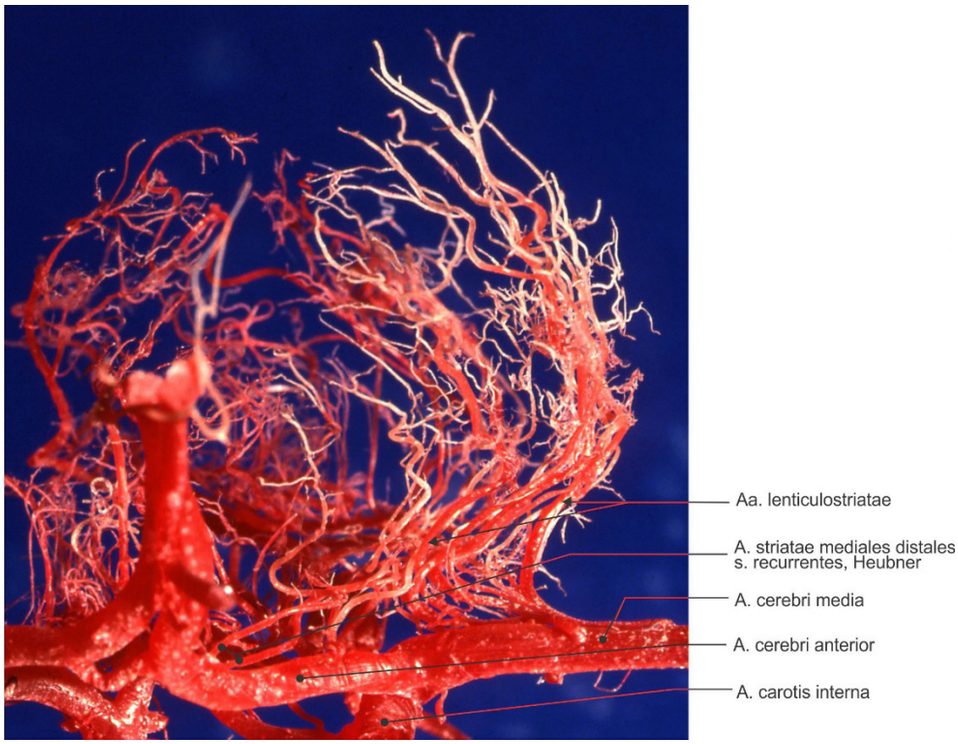

Figura 7. Degët perforante të ACM dhe ACA, e shikuar ventralisht (preparat koroziv) (S. Bexheti me bashkëpunëtor: „Atlas i diseksionit të njeriut“).

PËRFUNDIMI

Okluzioni i segmentit A1 të ACA jep më pak deficite neurologjike për shkak të ekzistimit të AcomA dhe qarkullimit kolateral nga ana e kundërt. Okluzioni i segmentit A2 rezulton me goditje ishemike dhe thirret si sindromi ACA. Rezulton me hemiparezë kontralaterale, si edhe me humbje kontralaterale të sensibilitetit, para së gjithash të këmbës, muskujve të pelvikut dhe perineumit, gjë që krijohet për shkak të ishemisë së lobulus paracentralis në faqen mediale të hemisferës. Mund të paraqitet edhe çrregullim i të folurit, të lexuarit dhe të shkruarit. Pacienti vështirë fillon të flasë, e ndërpret të folurën në mes të fjalisë, ka vështirësi në gjetjen e fjalëve dhe të ngjajshme. Çregullimet paraqiten përshkak të lezionit të fushës suplementare motorike të të folurit. Lezioni i corpus callosum sjell deri në apraksi dhe agrafi (19, 20, 21).

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Case report

GROENBLAD-STRANDBERG SYNDROME

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АПСТРАКТ

Вовед: Groenblad-Strandberg-ов синдром претставува нарушување на сврзното ткиво и се карактеризира со мултисистемска инволвираност, вклучувајќи ги примарно очите, кожата и кардиоваскуларниот систем. Тоа е ретка наследна болест, резултат на пореметување на еластинот, со преваленца од 1:25.000 до 1:100 000 кај општата популација.

Во трудот прикажуваме жена на 59 год. возраст со дијагностициран доминантен облик тип 1, познат како Pseudoxanthoma elasticum (PXE) со доста изразени ангиоидни стрии и промени во макулата, кардиоваскуларни атеросклеротски промени, кожни промени на вратот, аксијално, во антекубиталната фоса и параумбиликално.

Цел на трудот е преку приказ на случај да се презентира ова ретко мултисистемско наследно заболување и да се потенцираат современите модалитети на третман за компликациите кои може да се јават.

Заклучок: Сеуште не постои специфичен и ефективен третман за системските манифестации на PXE. Постојат ефективни терапевтски можности за окуларни компликации кои вклучуваат: ласер фотокоагулација (LFC), транспупиларна термотерапија, фотодинамска терапија (PDT), макуларна транслокациска хирургија и денес најчесто применуваниот метод со интравитреална апликација на анти – ВЕГФ препаратите.

Современиот пристап со периодични интравитреални анти ВЕГФ препарати даваат супресија на компликациите како хороидалната неоваскуларизација и макулопатија, со цел стабилизација на видот и спречување на тешки визуелни консеквенци.

Клучни зборови: псевдоксантома еластикум (PXE), Groenblad Strandberg – ов синдром, окуларни манифестации, ангиоидни стрии

ВОВЕД

Pseudoxanthoma elasticum (PXE) познат и како Groenblad-Strandberg синдром, е ретка наследна болест со проценета преваленца од 1: 25.000 до 1: 100.000 кај општата популација. (1) PXE се смета за прототип на мултисистемски ектопични нарушувања на минерализацијата и се карактеризира со аберантна минерализација на мекото сврзно ткиво, со дегенерација на еластичните влакна, вклучувајќи ги примарно очите, кардиоваскуларниот систем (КВС) и кожата.(2)

Клинички, вклученоста на очите, кожата, централниот нервен систем (ЦНС), срцето и ГИ-систем може да бидат присутни со варијабилна застапеност, како и периферната артериска болест.

Кожните лезии се состојат од мали, асимптоматски, жолтеникави папули или поголеми коалесцентни плаки, обично лоцирани на вратот и на области

на свиткување - кубиталната и поплитеалната јама, аксилата, во наборите од препоните и периумбиликалната површина.(2) Обично тие се првиот знак на PXE и го наговестуваат ризикот за развој на окуларни и други системски манифестации, а зафатената кожа станува лабава и збрчкана.(2)

Промените се детектираат во 2-рата или 3-тата декада од животот, а прогресијата е постепена и спорадична. (1)

Кардиоваскуларните манифестации вклучуваат калцификации во рамките на еластичното ткиво на интима и медиумите на крвните садови, што доведуваат до повремена клаудикација, коронарна и цереброваскуларна болест. (3) Може да бидат присутни валвуларни промени, најчесто пролапс на митралната валвула. Рана коронарна артериска болест поврзана со PXE е често тешка, во повеќето случаи се презентира како ангина пекторис или миокарден инфаркт. (3)

Окуларните манифестации на pseudoxanthoma elasticum вклучуваат промени како кора од портокал “peau d’orange”, ангиоидни стрии и хороидална неоваскуларизација.

Речиси 87% од пациентите со pseudoxanthoma elasticum имаат асоцирани ангиоидни стрии (AS). Ангиоидните стрии се појавуваат како пукнатини длабоко до васкуларната архитектура на ретината, потекнуваат од перипапиларната област и се протегаат зракасто од папилата на оптичкиот нерв, во сите правци.(4)

Компликација на ангиоидните стрии во окото е формирање на неоваскуларни мембрани во макулата на ниво на пигментниот епител - Брух-ова мембрана. Ова е слично на неоваскуларизацијата кај макуларна дегенерација поврзана со возраста (ARMD).

Доколку се најде хороидна неоваскуларизација (CNV) при клиничко испитување, флуоресцеинската ангиографија (ФФА) и оптичката кохерентна томографија (OCT) може да бидат корисни во разграничувањето, диференцирање и документирањето на локацијата и големината на неоваскуларната мембрана.

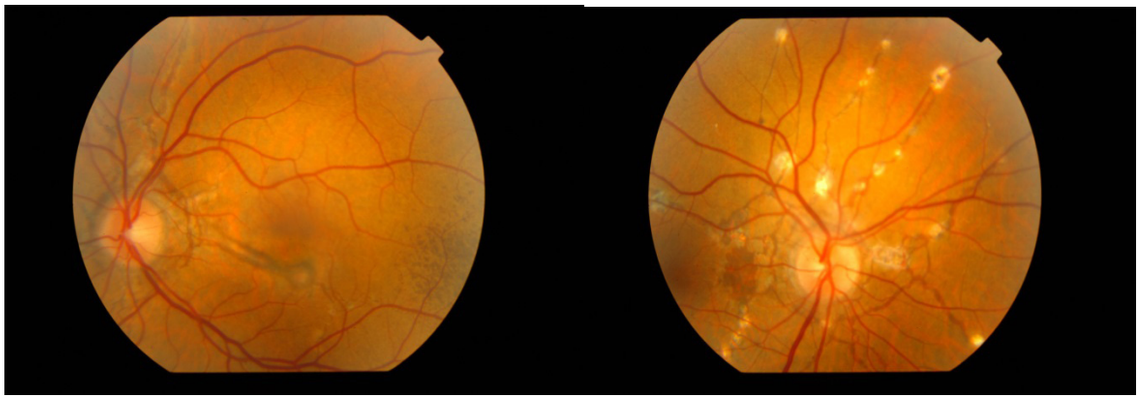
Приказ на случај

Жена, на 59 год. возраст, со најдобро корегирана видна острина (BCVA) движење на рака обострано, беше препратена на Универзитетската клиника за очни болести во Скопје за третман на поставена работна дијагноза сенилна дегенерација на макула, со хороидална неоваскуларизација.

По комплетниот офталмолошки преглед и извршените имиџинг следувања флуоресцеинска ангиографија (сл. 1, 2), оптичка кохерентна томографија со ангиографија (сл.3), како и во корелација со системските иследувања, се дијагностицира ова ретко метаболно наследно заболување, Groenblad - Strandberg Syndrome.

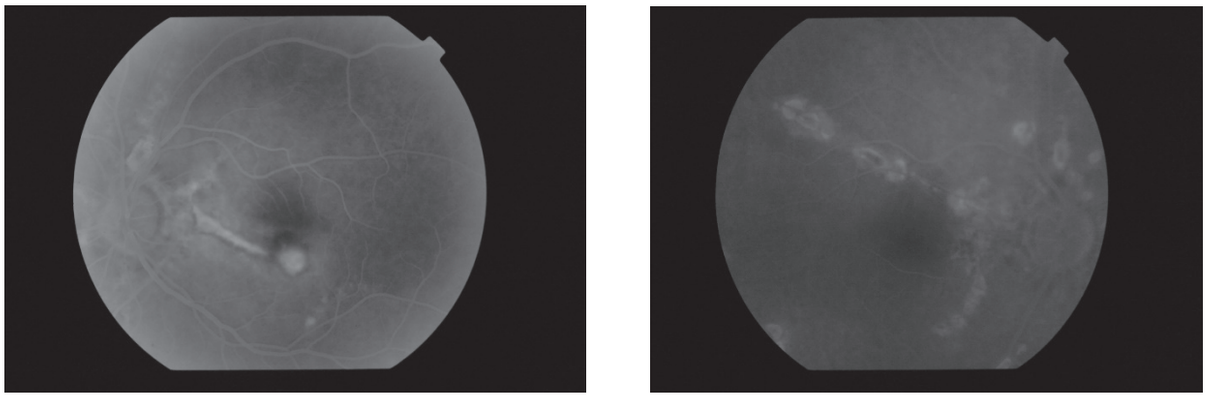
На клиничкиот преглед, се потврди дека пациентката има неколку големи кожни промени, симетрично распоредени на страните на вратот, аксилата и лактот со изразена набрчканост и олабавеност на кожата. (сл.4) Косата, ноктите и мукозните мембрани беа уредни.

Се доби податок за позитивна фамилна анамнеза каде братот и сестрата исто така имаат кожни промени, но без окуларни и други системски манифестации



а. б.

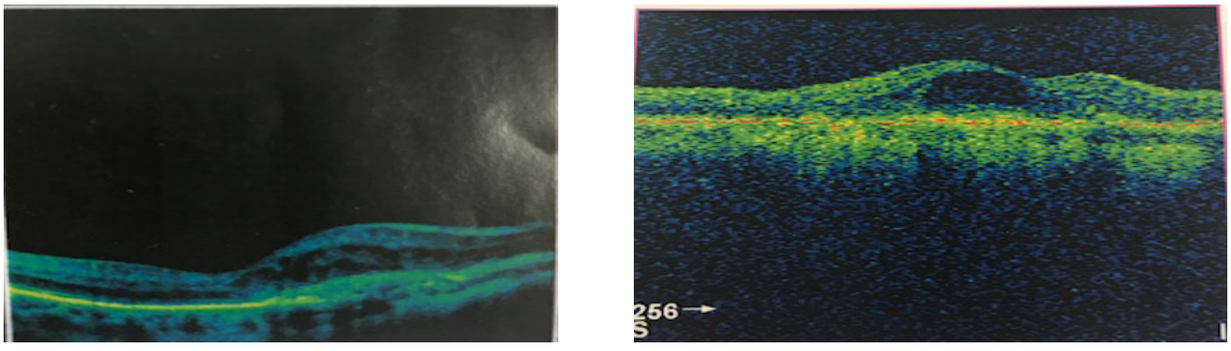
Сл. 1 Приказ на фундус фото а. наод на ретина на десно наод на ретина на лево око ангиоидни стрии, хороидална неоваскуларизација, фокални хориоретинални ожиљци



Сл. 2 Приказ на флуоресцеинска ангиографија, на лево и десно око хиперфлуоресценција поради дефект “феномен на прозорец” ангиоидни стрии, хороидална неоавскуларизација

По изведената оптичка кохерентна томогарфија со ангиографија на регијата на макула лутеа се дијагностицира доста напредната хороидална неоваскуларна мембрана поради што беше индициран третман со интравитреална апликација на Bevacizumab, анти ВЕГФ прешарат (Авастин). Се аплицираа три поединечни месечни дози интравитреално и се постигна регресија на наодот со стабилизација на видната острина. (сл. 3 а, б)

а. б.



Сл.4 Приказ на наод на оптичка кохерентна томографија на заден сегмент, пред и по апликација на анти ВЕГФ препарат Бевацизумаб, интравитреално

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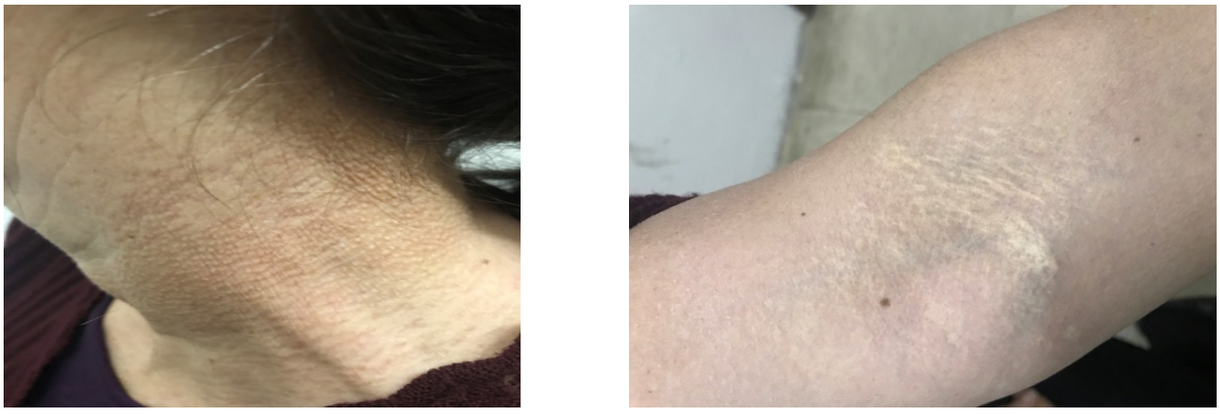

Сл. 4 Приказ на кожни промени а. набори на врат б. набори на антекубитална фоса

ДИСКУСИЈА

Pseudoxanthoma elasticum е исклучително ретко наследно заболување, со бавна прогресија и изразена мултисистемска инволвираност. PXE е предизвикана од мутации во ABCC6 (ATP - поврзувачка касетна подфамилија C член 6) генот кој го кодира трансмембранскиот ATP врзувачки ефлукс транспортер, кој нормално е изразен во црниот дроб и бубрегот.

Мутациите во аденозин трифосфатот (АТП), мултидисциплинарен протеински протеин 6 / ATP-поврзувачки касетна подфамилија C член 6 (MRP6 / ABCC6), кој е одбележан на хромозомот 16p13; се верува дека е водечка причина за ова нарушување. Концептот на PXE како системско метаболно нарушување, наместо чисто структурно нарушување на сврзното ткиво, произлегува од фактот дека генот ABCC6 енкодира за протеинот на целулатранспорт. (5) Сепак точниот механизам на ектопична минерализација останува во голема мера непознат. (2) PXE претставува наследно пореметување на еластинот, со проценета преваленца од 1:25.000 до 1:100.000. (1) Застапеноста е почеста кај женскиот пол и тоа 2 : 1, во однос на машкиот пол. (2) Постојат четири подтипови на ова заболување кои имаат окуларни манифестации, но со различен интензитет. Клиничките манифестации ретко се присутни при раѓање и обично се видливи во текот на втората или третата деценија од животот. (2)

Како два типа на автозомно доминантна pseudoxanthoma elasticum, се карактеризираат тип I - со класичен дистрибуиран осип, тешка и честа ангина при напор, интермитентна клаудикација, хипертензија, тежок хороидоретинитис и слепило. Тип II е многу поблага форма, со макуларен осип, без васкуларни промени и блага ретинална дегенерација. (6)

Автозомно – рецесивен pseudoxanthoma elasticum, исто така, има два вида: рецесивен тип I со кожен осип, умерено тешка ретинална болест и одредена предиспозиција за гастроинтестинално крварење, и рецесивен тип II кој е многу поредок, влијае на целата кожа која е лабава со интензивно инфилтрирани промени и дегенерирани еластични влакна. (7). Клиничкиот ентитет за прв пат е опишан од страна на францускиот дерматолог Ригал (Rigal), во 1881 година, додека Фердинанд-Жан Дариер (Ferdinand-Jean Darier) го формулира терминот pseudoxanthoma elasticum, во 1896 година, обележувајќи го сврзното нарушување како патогномичен знак, различен од ксантомите (па оттука и називот псевдоксантом). (2)

Ангиоидните стрии на ретината првично се опишани од Роберт Дојн (Robert W. Doyne) и од Ото Пфланже (Otto Pflange) во 1889 и 1892. (2) Во 1929 год., двајца шведски лекари, офталмологот Естер Гроенблад (Ester Gröenblad) и дерматологот Џејмс Страндберг (James Strandberg), први ја дефинираат поврзаноста помеѓу ангиоидните стрии и псевдоксантома еластикум и го даваат терминот Гроенблад - Страндберг синдром (Gröenblad - Strandberg syndrome), кој се користи како синоним за PXE со изразен офталмолошки наод (2)

Бакарани Контри (Baccarani Contri) со соработници покажале дека еластичните влакна имаат зголемена експресија на нормални конститутивни протеини и се акумулираат аберантни матрични протеини познати по нивниот висок афинитет за калциум, вклучувајќи се во процесите на минерализација како алкална фосфатаза, коскено сијалопротеин и остеонектин. (8) Офталмолошките карактеристики на PXE вклучуваат првенствено peau d'orange, ангиоидни стрии, хороидална неоваскуларизација (CNV), хеморагии и формирање на лузна. (2) (4)

"Peau d'Orange" или "кора од портокал" е најраната фундускопски видлива промена кај пациентите со PXE, која претходи на развој на ангиоидните стрии. Претставува назив за билатерални пигментирани промени, темни дамки на заден пол, обично темпорално од макулата или на средна периферија. (1) (2). Ангиоидните стрии се најочигледни, конзистентни абнормалности кај PXE фундусот. (2) Тие се претставени како нерегуларни остри линии, со кафеаво-сива боја, кои зрачат концентрично од перипапиларниот прстен кон периферијата. Хистопатолошки ангиоидните стрии претставуваат тракасти дехисценции во еластичниот слој на Бруховата мембрана заради патолошката кршливост на базалната ламина, обично резултат на комбинација на дегенеративен процес и депонирање на калциум. (1) (2) (4)

Хороидална неоваскуларизација (CNV) претставува најсериозна компликација на ангиоидните стрии и се јавува во 72 - 86% од случаите, како што е и во нашиот случај. (сл. 3а) (1) CNV на макуларната регија е честа компликација кај пациенти со PXE и доведува до субретинални хеморагии, ексудација и фиброваскуларна форма на лузна, со последователна

загуба на визуелната острина. (сл.3а) (2) (9) (10) Дополнително, пациентите со PXE имаат зголемен ризик од развој на друзи на папилата на оптичкиот нерв. Точниот механизам е нејасен, но веројатно е поврзан со абнормална минерализација на lamina cribrosa.(2). Растегната кожа, срцеви промени и хороидните стрии се знаци кои pseudoxanthoma elasticum го диференцираат од Ehlers-Danlos-овиот синдром тип 6. (11) (12)

Јувенилната Paget - ова болест е поврзана со прогресивна ретинопатија, која се карактеризира со бледило на оптичкиот диск, промени на ретината на пигментниот епител и последователен развој на ангиоидни стрии, што може да биде комплицирано со хороидална неоваскуларизација, како предоминантна причина за визуелна загуба. Ангиоидните стрии се во корелација со Paget овата болест кај околу 2 % и се смета дека калциумот се врзува за еластинот на Bruch-овата мембрана, што ја зголемува фрагилноста. Истовремено преовладуваат скелетни манифестации, од каде и се диференцира од Groenblad Strandberg синдромот. (11) (12)

Кардиоваскуларните манифестации кај пациенти со PXE се бројни и вклучуваат редуциран периферен пулс, хипертензија (HTA), ангина пекторис и интермитентна клаудикација. Често се присатни и гастроинтестинални хеморагии, манифестирани како хематемеза и мелена. Пациентите со PXE, можат да развијат и предвремена атеросклероза со рани акутни миокардни инфаркти и цереброваскуларни инсулти. (2) (1) Прикажани се случаи со смртен исход, како последица од кардиваскуларните компликации. (1,2)

ЗАКЛУЧОК

Сеуште не постои специфичен и ефективен третман за системските манифестации на PXE Постојат ефективни терапевтски можности за окуларни компликации, кои вклучуваат: ласерска фотокоагулација (LFC), транспупиларна термотерапија, фотодинамска терапија (PDT), макуларна транслокациска хирургија и интравитреална апликација на анти-ВЕГФ препарати. Последнава деценија супресија на компликациите како хороидалната неоваскуларизација и макулопатија, може да се постигне со периодични интравитреални анти-VEGF апликации, со цел стабилизација на видот.

Сите клинички манифестации во кожата, очите и артериските крвни садови, се последица на таложење на калциум фосфат во еластични влакна. Со навременото дијагностицирање и современиот терапевтски пристап ќе се спречат тешки визуелни консеквенци.

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Case report

АЛЕРГИЧНА РЕАКЦИЈА НА ПРОТАМИН КАКО СОСТАВНА КОМПОНЕНТА НА ИНСУЛИН

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АБСТРАКТ

Увод: Дијабет мелитус е метаболна болест која се карактеризира со хипергликемија која настанува поради нарушена секреција на инсулинот или поради нарушено дејствување на инсулинот. Хронични компликации на дијабетесот се јавуваат после повекегодишно траење на болеста, а кај нерегулирани метаболни пореметувања тие се јавуваат и порано. Пациентка на 67 години,боледува од Дијабетес мелитус Тип 2,последниве 5 години. Во Центар за дијабет се јавува поради нерегулирани гликемии и појава на алергична реакција по апликација на инсулинската терапија Humulin N ,NPH U-100 Insulin (Isophane Susp). Поради увид на хематоми и уртикароидни промени во пределот на надлактици, натколеници и абдомен, поточно на местата на апликација на инсулинската терапија проследени со печење и пруритус, извршена е промена на инсулинот во Детемир инсулин. Се појавувала иста реакција, но во помал степен и интензитет. По една недела е извршен контролен преглед при што е увидено дека има помали хематоми на местата на апликација на инсулинската терапија без појава на печење и чешање.Упатена е на дерматовенерологија Градска Општа болница каде е хоспитализирана. Метод: patch na ESP; prick test; Intradermalen test; биохемиски анализи, имунолошки анализи, гликемичен профил. Утврден алерген е протамин како составна субстанција на инсулините. Препорака- да се продолжи лекувањето со инсулин Гларгине 30 И.Е. субкутано еднаш дневно и игли Новопен 6 мм. Дискусија : Алергијата на инсулин и резистенцијата на инсулин се посредувани од антитела. Антителата од класата на имуноглобулинот Е посредуваат во рана локална реакција во системски реакции како и во некои облици на касни реакции. Локалните реакции после 8-24 часа од апликацијата на инсулин се предизвикани од подоцнежен тип на пречувствителност на самиот инсулин или од цинкот и протаминот во него.Честата алергија на инсулинот е сè помала од година во година, веројатно поради употребата на пречистените форми на хумани инсулини. Етиолошкиот агенс е непротеински дел од инсулинот (протамин или цинк) или неинсулински протеин. Протамините се мали, нуклеарни протеини богати со аргинин, кои ги заменуваат хистоните доцна во хаплоидната фаза на сперматогенезата и се верува дека се од суштинско значење за кондензација на сперматозоидите и стабилизација на ДНК.Заклучок:Кога се мешаат со инсулин, протаминте го забавуваат почетокот и го зголемуваат времетраењето на дејството на инсулинот. Локалните реакции после 8-24 часа од давање на инсулин се предизвикани од подоцнежен тип на пречувствителност на самиот инсулин, цинкот или протаминот во него.

Клучни зборови :Протамин,Дијабет Мелитус тип 2,алергија на инсулин.

ВОВЕД

Дијабетес мелитус е метаболна болест која се карактеризира со хипергликемија која настанува поради нарушена секреција на инсулинот или поради нарушено дејствување на инсулинот или комбинирано. Пропратен е со пореметен метаболизам на масти и белковини, а кога болеста не е регулирана пореметен е метаболизмот на вода и електролити како и ацидобазната рамнотежа.Постојат повеке типови на Дијабет. Дијабет тип 1 се јавува како резултат на недостаток на инсулин и има тенденција кон кетоза. Дијабет мелитус тип 2 претставува хетерогена група на пореметувања која обично се карактеризира со различен степен на инсулинска резистенција, нарушено лачење на инсулин и зголемена концентрација на гликоза во крвта. Препознавањето на различни патогенетски процеси кај ДМ тип 2 има

важно терапевтско значење.

Хронични компликации на дијабетесот (ХДК) се јавуваат после повекегодишно траење на болеста, а кај нерегулирани метаболни пореметувања тие се јавуваат и порано. ХДК се делат на микроангиопатски компликации –дијабетична ретинопатија, нефропатија и невропатија и на макроангиопатски, кај кои главниот фактор е забрзан процес на атеросклероза -артериска хипертензија, коронарна болест, болест на крвните садови на ЦНС и болест на длабоките вени на долните екстремитети. Преваленцата на коронарната болест кај особи со нормална гликемија е 9 проценти, а кај особи со дијабетес 20 проценти. Патофизиолошки промени кај пациентите со дијабетес вклучуваат дисфункција на ендотелот, изменета активност на тромбоцитите како и микроалбуминемија.Акутниот коронарен синдром(АКС) е збир на симтоми кои се последица на акутна миокардна исхемија и представува животно загрозувачка манифестација на атеросклероза на коронарните артерии. Опфаќа нестабилна ангина пекторис, инфаркт на миокардот со СТ елевација (СТЕМИ), инфаркт на миокардот без СТ елевација (НСТЕМИ) и напрасна срцева смрт. Основен патохистолошки супстрат АКС представува нестабилен атеросклеротичен плак со тромбоза.

Дијабет мелитус денес е едно од најчестите хронични заболувања со тенденција на понатамошен пораст на зачестеност но и еден од главните причини за зголемен број на заболени од кардиоваскуларни болести. Светската здравствена организација-СЗО и Меѓународната федерација за дијабетес - ИДФ проценуваат дека во светот од Дијабет Мелитус боледуваат 430 милиони луѓе. Во Македонија 11 проценти од населението се болни од дијабет,со тенденција на пораст. Бројот на кардиоваскуларни компликации од дијабет е на прво место за причина за морбидитет и морталитет во Македонија .

Приказ на случај

Пациентка на 67 години, боледува од Дијабетус мелитус Тип 2 последниве 5 години. Поради недоволна гликорегулација, пациентката од орална антидијабетична терапија од септември 2018 год е префрлена на инсулинска терапија со Humulin N-NPH U-100 Insulin (Isophane Susp) 2 пати дневно. Во Центар за дијабет се јавува поради нерегулирани гликемии и појава на алергична реакција по апликација на инсулинската терапија. Алергичната реакција била проследена со појава на уртикарија на која пациентката не и придавала значење, сфаќајки ја како адаптација на инсулинот. Побарала промена на инсулинската терапија кај матичениот дијабетолог, но тој одбил да ја смени. По 6 месеци побарала промена на инсулинот кај друг дијабетолог. Поради увид на хематоми и уртикароидни промени во пределот на надлактици, натколеници и абдомен, поточно на местата на апликација на инсулинската терапија проследени со печење и пруритус, како и поради нерегулирана гликемија на гладно (утрински гликемии на гладно мерени три пати неделно 9,7:12;13,2;10,5;14;10;12.3;11,9;10;12,3;13,8(табела 1) и високи вредности на гликолизиран хемоглобин ХБА1Ц- 8,9% (табела 1) извршена е промена на инсулинската терапија во базален инсулин Детемир 30 единици дневно како и промена на инсулинските игли од инсупен во новофине од страна на новиот дијабетолог. На следната контрола по една недела констатирана е појава на слични реакции но во помал степен и интензитет, без појава на печење и чешање. Гликемија на гладно со подобрени вредности 9,1;8,2 ;6.9 ;7,8 ;7,2 .(табела 1)Упатена е на дерматовенерологија во Градска Општа болница каде е хоспитализирана.

Вредности на утринска гликемија со различни инсулини се покажани во табела 1

	Утринска гликемија на гладно	ХБА1Ц
Со инсулин Изофан	9,7:12;13,2;10,5;14; 10;12.3;11,9;10;12,3;13,8	8,9%
Со инсулин Детемир	9,1;8,2 ;6.9 ;7,8 ;7,2	

Од пропратни коморбидитети, пациентката боледува од коронарна инсуфициенција, дислипидемија и хипертензија артериалис. По препорака на специјалист кардиолог е поставена на орална антикоагулантна терапија(ОАТ). Од останатата фармаколошка анамнеза на хронична терапија е со tbl Acenocoumarol 4 mg по шема, tbl Digoxin 0,25 mg 1x1, tbl Spirinolacton a 100mg 1x1/2, tbl Furosemide a 500mg 1x ¼ , tbl Bisoprolol a 5mg 1+0+1/2, tbl Atorvastatine a 40 mg 1x1, tbl Lerkanidipin 10mg 2x1/2 , tbl Losartan a 50 mg 1x1 tbl Metformin a 1g 1x1. Мерени утрински гликемии 7,9;8,1;9,5 ;8,4;7,7; 8,6 ;8.2ммол/л додека вечерни гликемии 12,5 ;7,8 ; 9,7 ;11,1 ;7,9;12.3 ;7,3 .

Во текот на хоспитализацијата е направен patch na ESP кои по 24 часа останаа негативни.(табела 2) Направени се и prick test I intradermalen test na insulin Novomix

30 flex pen; Insulin Insuman comb 25 –solostar, Insuman rapid -solo star кои по 20 мин беа позитивни (ПАУЛО уртики).(табела 2) Prick I Intradermalen test на insulin Lantus е негативен.(табела2) ASST е негативно. (табела 2)После инсулините се направи и тест боцкање со игла Novopen 6mm. (табелан2)Со Новопен игла алергичната реакција е минимална. Алерголошка анамнеза CAVE фластер.(табела 2) Негира болести на зависност ,сексуално преносливи болести и Туберкулоза.

Дијагностички алерголошки испитувања се прикажани во табела 2

	prick test	intradermalen test	Тест боцкање со инсулинска игла	Алергија на фластер	ACCT	Алергија на протамин	Patch na ESP
na nsulin Novomix 30 flex pen	позитивен	позитивен					
Insulin Insuman comb 25 – solostar	позитивен	позитивен					
Insuman rapid -solo star	позитивен	позитивен					
Insulin Glargine	негативен	негативен					
Novopen 6мм igla			Негативно				
Фластер				Позитивно			
ACCT					Негативно		
Алергија на протамин						Позитивно	
Patch na ESP							негативни

Од иследувањата ККS;RDW%=16,7референтни вредности(11-16);Биохемиски анализи ;acidum uricum 598umol/lреферентни вредности (172-405); trigliceridi 2,48 референтни вредности (0,3-1,7); HBA1C 58,6mmol/lрефрентни вреднсти (24-43);urea11,2mmol/l референтни вредности (2,8-7.2); glikoza 6,6 mmol/l референтни вредности (3,6-6,4); Hdl 0,66mmol/l референтни вредности(1,04-2).AST;ALT;kreatinin, bilirubin totalen,K,Cl;Na;,bilirubin direkten, holesterol, albumin, calcium, magnesium,serumsko zelezo, се б.о(во граници на нормални референтни вредности).(Табела 3)Имунолошки анализи; RF 18,8 IU/ml референни вредности (0-15,9);ASLn603IU/ mlреферентни вредности(0-214)Вредности за ЦРП ИгГ,ИгА,ИгМ,Ц3,Ц4,феритин .ИгЕ,Хеликобактер пилори Иг Г се бо.Хормонален статус и туморски маркери PTH 134 pg/ml референтни вредности (12-65); вредности на TSH ,T43 I T3, anti TPO,AFP,CEA,CA15-3,CA19-9,CA125 се б.о. Урина доста Le , протеини во трагови,uro0,2E.U/dl; Тестови за хемостаза:PT 27,INR 2,4;Fibrinogen 4,6g/l;d dimeri 0,17mg/l.(Табела 3)

Дијагностички биохемиски и имунолошки испитивања се прикажани во табела 3

	референтни вредности	резултат
Биохемиски анализи		
RDW%	(11-16);	16,7
acidum uricum umol/l	(172-405)	598
trigliceridi	(0,3-1,7)	2,48
HBA1C	(24-43)	58,6
Glikemija	(3,6-6,4)	6,6
Urea(mmol/l)	(2,8-7.2)	11,2
Hdl	(1,04-2)	0,66
Имунолошки анализи		
RF IU/ml	(0-15,9)	18,8
ASLnIU/m	(0-214)	603
Хормонален статус		
PTH pg/ml	(12-65)	134
Тестови на хемостаза		
PT		27
INR		2,4

Fibrinogen g/l		4,6g
dimeri mg/l		0,17
Уринарни тестови		
Протеини во урина	негативно	Во трагови
uroE.U/dl		0,2

Препорака- да се продолжи лекувањето со инсулин Гларгине 30 И.Е. с.к. наутро и игли Новопен 6 мм.За новооткриениот Гихт ординирана е терапија тбл Алопуринол 100мг еднаш дневно и диета без конзумација на (црвено месо, алкохол и изнутрици ,спанаќ ,грав).Поради зголемените вредности на PTH,RF I ASL се упатува во центрите за остеопороза. Утврден алерген е протамин како составна супстанција на испитаните инсулини.По две недели пациентката се јави на контрола. Немаше алергични промени и гликемијата беше задоволителна (7,2;8,3;6,9;5,9;7,2). Закажана е контрола по еден месец.

ДИСКУСИЈА

Уртикарија е сериозна алергиска реакција која започнува ненадејно.Обично се манифестира со одредени симптоми, вклучувајќи исип или уртика кој чеша, оток и печење. Вообичаени причинители се убоди од инсекти, храна и лекови.Оваа алергична реакција е резултат на ослободување на протеини од одредени видови на бели крвни клетки. Овие протеини се супстанции што можат да ја отпочнат или да ја влошат алергиската реакција. Нивното ослободување може да биде предизвикано или како реакција на имунолошкиот систем или од друга причина која не е поврзана со него.

Алергичната реакција може да биде предизвикана од реакција на организмот на било која туѓа супстанца. Храната е највообичаена причина кај деца и млади луѓе. Лековите и убодите од инсекти се повообичаени кај повозрасните. Помалку вообичаени причини се физички фактори, биолошки агенси (на пр. сперма), латекс, хормонални промени, адитиви во храната (на пр. мононатриум глутаминат и прехранбени бои) и лекови за надворешна употреба (топикални лекови). Исто така, вежбањето или надворешната температура (и висока и ниска) можат да предизвикаат алергија, со тоа што ќе доведат до ослободување на хемикалии од клетките на одредени ткива (познати како мастоцити), кои ја отпочнуваат алергиската реакција. Често алергичната реакција која е последица од вежбање е поврзана со јадење на одредена храна. Доколку алергичната реакција се јави додека лицето прима анестезија, највообичаени причини се одредени лекови кои предизвикуваат парализа (невромускулни блокатори), антибиотици и латекс. Кај 32-50% од случаите причината е непозната (идиопатска алергија).

Секој лек може да предизвика алергична реакција. Најзастапени се бета-лактамските антибиотици (како пеницилин), потоа аспирин и нестероидни антиинфламаторни лекови(НСАИЛ). Други вообичаени причини за алергија се хемотерапија, вакцини, протамин и лекови од растително потекло. Некои лекови, како што се ванкомицин, морфиум и лекови што се користат за подобрување на рендгенските снимки (радиоконтрастни агенси) предизвикуваат анафилакса со тоа што оштетуваат одредени клетки во ткивата, доведувајќи до ослободување на хистамин (дегранулација на мастоцити).Анафилакса на пеницилин или цефалоспорин се јавува откако тие ќе се врзат со протеините во телото, а некои се врзуваат полесно. Анафилакса на пеницилин се јавува кај секои 2.000 до 10.000 лекувани луѓе. До смрт доаѓа помалку од еднаш на секои 50.000 лекувани луѓе. Анафилакса на аспирин и НСАИЛ се јавува еднаш на секои 50.000 луѓе.Ако некој има реакција на пеницилин, постои поголем ризик дека ќе има реакција и на цефалоспорин, но сепак ризикот е помал од 1 во 1.000 случаи. Постарите лекови што се користеле за да ги подобрат рендгенските снимки (радиоконтрастните агенси) предизвикуваат реакција кај 1% од случаите. Понови лекови со понизок осмоларен радиоконтрастен агенс предизвикуваат ракција кај 0,04% од случаите.

Фактори на ризик: Луѓе со атописки болести како астма, егзем или алергиски ринитис имаат висок ризик од алергична реакција од храна, латекс и радиоконтрастни агенси. Кај овие луѓе ризикот не е зголемен од инјектирани лекови и убоди од инсекти. Едно истражување покажало дека 60% од децата со анафилакса имале историја од претходна атописка болест. Повеќе од 90% од децата кои умираат од анафилакса имаат астма. Ризикот е зголемен кај луѓето што имаат нарушувања предизвикани од премногу мастоцити во ткивата (мастоцитоза). Колку подолго време е поминато од последното изложување на агенсот кој ја предизвикал анафилаксата толку е помал ризикот од нова реакција.

Механизми:Анафилаксата е сериозна алергиска

реакција што започнува ненадејно и опфаќа многу органски системи.Таа се јавува поради ослободување на воспалителни посредници и цитокини од мастоцитите и базофилите. Нивното ослободување обично се јавува како резултат на реакција на имунолошкиот систем, но може да биде предизвикано и од оштетување на овие клетки, што не е поврзано со имунолошка реакција.

Имунолошки:Кога анафилаксата е предизвикана од имунолошка реакција, имуноглобулинот Е (ИгЕ) се врзува со туѓа материја која ја започнува алергиската реакција (антиген). Комбинацијата на врзување на ИгЕ за антиген ги активира ета-рецепторите за Fc (FcFcεRI) на мастоцитите и базофилите. Мастоцитите и базофилите реагираат со ослободување на воспалителни посредници, како што е хистаминот. Овие посредници го зголемуваат контрахирањето на бронхијалните мазни мускули, предизвикувајќи проширување на крвните садови (вазодилатација), го зголемуваат пропуштањето на течности надвор од крвните садови и ја намалуваат работата на срцевиот мускул. Исто така, постои имунолошки механизам кој не е зависен од ИгЕ, но не е познато дали ова се случува кај луѓето.

Неимунолошки:Кога анафилаксата не е предизвикана од имунолошка реакција, реакцијата е предизвиката од агенс што директно ги оштетува мастоцитите и базофилите, предизвикувајќи ги да лачат хистамин и други супстанци што вообичаено се поврзани со алергиска реакција (дегранулација). Агенсите што можат да ги оштетат овие клетки се контрастно средство за рендген, опиоиди, температура (топло или ладно) и вибрации.

Честата алергија на инсулинот е сè помала од година во година, веројатно поради употребата на пречистените форми на хумани инсулини. Алергијата на инсулин и резистенцијата на инсулин посредувани се со антитела. Антителата од класата на имуноглобулинот Е посредуваат во рана локална реакција во системски реакции како и во некои облици на касни реакции. Антителата од класата на имуноглобулин G предизвикуваат резистенција на инсулин, Н тип на преосетливост и некои локални форми на подоцнежна преосетливост (реакција после 4-12 часа од внесувањето на инсулин). Блокирачките антитела од класата на имуноглобулин Г се појавуваат кај пациенти кај кои инсулин десензибилизацијата е извршена. Локалните реакции после 8-24 часа од давање на инсулин се предизвикани од подоцнежен тип на пречувствителност на самиот инсулин или од цинкот во него.

Етиопатогенеза: Етиолошкиот агенс е непротеински дел од инсулинот (протамин или цинк) или неинсулински протеин. Почеста е алергија на самиот инсулин. Говедскиот инсулин е најмногу алерген, помалку алерген е свинскиот инсулин, а хуманиот инсулин е најмалку алерген.

Инсулинот е пептид кој се состои од 51 аминокиселина, а е изграден во форма на два ланци, меѓусебно поврзани со два дисулфидни моста. Порано инсулинот се добивал со екстракција од говедски или свински панкреас. Секако , таквиот инсулин не бил најефикасен, иако незначајно се разликувал од човечкиот. Проблемот бил во тоа што тој инсулин содржел и примеси на другите структури на панкреасот, при што можело да се појават силни и по живот опасни алергиски реакции. Денес, инсулинот се произведува како чист хуман инсулин со технологија на рекомбинантна ДНК (производство со помош на генетски модифицирани бактерии Escherichije coli). Инсулинот може да се врзува со цинк при што се создаваат димери или доаѓа до создавање на уште поголеми агрегати.Се применува парентерално и супкутано - под кожа. Некогаш користењето на инсулините бараше употреба на шприц и игла, но денес речиси сите инсулински препарати се применуваат со помош на пенкало во форма на пенкало - «Pen systems». Оваа апликација е практична за секојдневните инјектирања, многу едноставна и стерилна.Во чист облик инсулинот започнува брзо да функционира - веќе по половина час. Меѓутоа, најчесто е потребно да се има инсулин кој брзо дејствува, но дејството да се задржи за подого време.Според брзината, интензитетот и траењето на дејствотоинсулините ги делиме на 4 групи:

- Инсулини со брзо дејство - содржи само инсулин или лиспро-инсулин

- Инсулини со среднодолго дејство - содржат протеин протамин и инсулин НХП-инсулин

-Инсулини среднодолго дејство со брзо појавување на дејството - содржат комбинации на чист инсулин и НХП-инсулин

- Инсулини со долго дејство - т.н. “Ултраленте инсулин” или инсулин-гларгин.

Различни комбинации на инсулин, цинк, протамин и

пуфери денес може да се направат препарати на инсулин со точно определени брзини на дејство, интензитет и времетраење на дејството. Лиспро-инсулин е вештачки инсулин со изменет редослед на аминокиселините кои неверојатно брзо дејствува. Инсулин-гларгине, новиот облик на базален долгоделувачки инсулин е пегилиран инсулин, што всушност претставува инсулин-депо. NPH insulin (neutralni protaminski Hagedorn, izofanski insulin) е брзодеолувачки инсулин кој се користи за подобрување на гликемичната контрола.Тој се произведува со помош на генетски модифицирана бактерија Escherichia coli. Хумаката суспензија на инсулин изофан се состои од кристална суспензија на хуман инсулин со protamin и cink. Таквата комбинација му дава на интермедиерно делувачкиот инсулин спор почеток на дејството и подолго траење од нормалниот човечки инсулин.

Протамините се мали, нуклеарни протеини богати со аргинин, кои ги заменуваат хистоните доцна во хаплоидната фаза на сперматогенезата и се верува дека се од суштинско значење за кондензација на сперматозоидите и стабилизација на ДНК. Тие можат да дозволат погусто пакување на ДНК во сперматозонот од хистоните, но тие мора да бидат декомпресирани пред генетските податоци да можат да се користат за синтеза на протеини. Меѓутоа, кај луѓето, а можеби и други примати, 10-15% од геномот на спермата е спакуван од хистони кои се сметаат за врзување на гените кои се неопходни за раниот ембрионски развој.Протамините протеамин и протеамин (ПЛ) се меѓу нуклеарните основни протеини специфични за спермата (СНБП). ПЛ протеините се меѓупроизводни во структурата помеѓу протамин и Хистон Н1, чијшто С-терминал е претходник на ртење на протаминот. Протамин се користи во кардиохирургија, васкуларна хирургија и интервентни радиолошки постапки за неутрализирање на ефектите на хепарин против коагулација. Несаканите ефекти вклучуваат зголемен притисок на пулмоналната артерија и намалување на периферниот крвен притисок, потрошувачка на миокарден кислород, срцеви излез и отчукувања на срцето. Протамин сулфат е антидот за предозирање со хепарин, но може да настане тешка алергија. А синцирот скратена верзија на protamine, исто така, делува како потентен антагонист на хепарин, но со значително намалена антигенност. Првично беше произведена како мешавина направена од термолизин дигестија на протамин, но вистинскиот ефективен пептиден дел VSRRRRRRGGRRRR оттогаш е изолиран. Аналог на овој пептид е, исто така, произведен. Во генската терапија, способноста на протамин сулфат за кондензација на плазмидна ДНК, заедно со нејзиното одобрување од страна на американската администрација за храна и лекови (ФДА), го направи привлечен кандидат за зголемување на стапките на трансдукција од страна на двете вирусни и невирусни (на пр. Користење на катјонски липозоми) со посредство на механизми за испорака.Протамин може да се користи како лек за спречување на дебелина. Протаминот се покажа дека ги одвраќа зголемувањата на телесната тежина и липопротеините со ниска густина кај стаорци со висока масленост. Овој ефект се јавува преку инхибиција на активноста на липазата, ензим одговорен за варење и апсорпција на триацилглицерол, што резултира со намалување на апсорпцијата на диеталната маст. Нема оштетувања на црниот дроб кога стаорците биле третирани со протамин. Сепак, емулзификацијата на масни киселини со долг синџир за варење и апсорпција во тенкото црево е помалку константна кај луѓето отколку стаорци, што ќе ја разликува ефективноста на протамин како лек. Понатаму, човечките пептидази може да го деградираат протаминот со различни стапки, така што се потребни дополнителни тестови за да се утврди способноста на протаминот за спречување на дебелината кај луѓето.

ЗАКЛУЧОК

Кога се мешаат со инсулин, протамините го забавуваат почетокот и го зголемуваат времетраењето на дејството на инсулинот (види NPH инсулин). Локалните реакции после 8-24 часа од давање на инсулин се предизвикани од подоцнежен тип на пречувствителност на самиот инсулин, цинкот или протаминот во него.

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Case report

PATIENT WITH ANCYLOSING SPONDYLITIS –BECHTEREV DISEASE AND FRACTURE OF C4, C5 WITH PRIMARILLY QUADRIPLEGIA

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ABSTRACT

The ankylosing spine is usually prone to fracture after minor trauma so, as usually our patient fell down on ice in skiing center Popova Sapka and he got a big pain in cervical spine immediately without neurological deficit in first moments after injury. He had a fast transport with solid immobilization of the cervical spine on a special table to a Traumatology clinic in Skopje. While he arrive in Skopje we detected a complete quadriplegia, and he was admitted on Trauma department with such a diagnosis. He was received in Intensive care unit and we perform Usually RTG investigation, CT-scan and MRI of cervical spine. We found complete disruption on level C4, C5 with soft tissue compression on spinal canal from the posterior side. We prepare the patient for posterior approach because in such cases anterior approach is not possible because of the stiffness of cervical spine, also the compression was from posteriorly, and we use special elastic canilla for intubation and perform a decompression and posterior fixation Synapsis system two levels above and two levels below. In such patients with ankylosant spondylitis – Bechterev disease and fracture of cervical spine we can recommend usually posterior approach because of the stiffness of the cervical spine and limited chances for performing the anterior approach. We can also recommend decompression combined with posterior fixation. Anesthesiologists have to use flexible canilla for intubation. Chances for neurological recovery are bigger if the decompression is immediately done.

Key words: Akylosing spondylitis – Bechterev disease, Free of CIV, CV, primarily quadriplegia

INTRODUCTION

The ankylosing spine is usually prone to fracture after minor trauma so, as usually our patient fell down on ice in skiing center Popova Sapka and he got a big pain in cervical spine immediately without neurological deficit in first moments after injury. He had a fast transport with solid imobilisation of the cervical spine on a special table to a Traumatology clinic in Skopje. While he arrive in Skopje we detected a complete quadriplegia, and he was admitted on Trauma department with such a diagnosis.

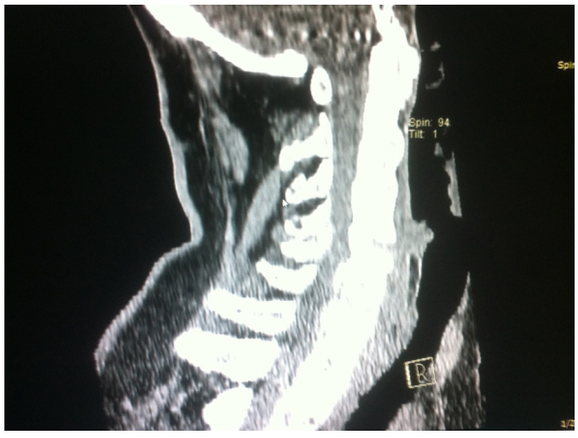
Several authors have shown that patients with ancylosing spondylitis have a bigger fracture risk compared to unaffected individuals. In those patients fusion of sacroiliac joints and spine occurs due to chronic inflammation followed by generalized stiffness of the spine. This disease is very rare and have a prevalence of 0,1 -1,4% and usually affect males in younger than 30 years., but our patient have 67.

Case report

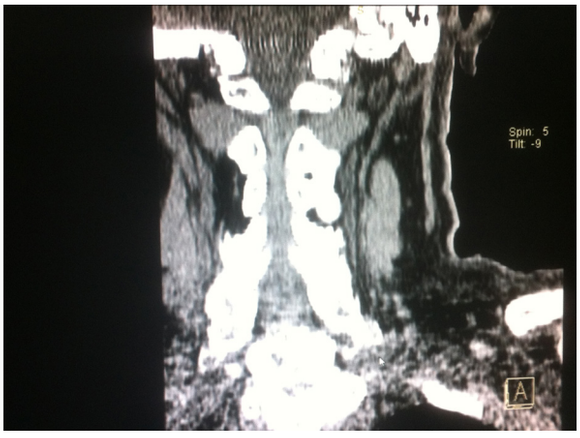
He was received in Intensive care unit and we perform Usually Rtg investigation, CT-scan and MRI of cervical spine. We found complete disruption on level C4,C5 with soft tissue compression on spinal canal from the posterior side. Fractures in ankylosed spine are often unstable due to the ossification of supportive and elastic soft tissues and often they can cause neurologic deficit as a result of dislocation. Neurologic deficit after fracture is well known and feared complication in ankylosing spondylitis, therefore this patients should be handled with great care even and especially when a fracture is suspected. We found a complete motor deficit in the both legs and only possible movements in elbows and humeroscapular region. Sensitive sensations absent below the both mammilla's. Babinski positive on both legs. Bradycardia, Spinal shock.

We prepare the patient for posterior approach because in such cases anterior approach is not possible because of the stiffness of cervical spine, also the compression was from posteriorly, and we use special elastic canilla for intubation and perform a decompression and posterior fixation Synapsis system two levels above and two levels below.

After the operation we perform control MRI for visualizing of performed decompression and he receive Thromoprophylaxis with LMWH according to ACCP. Also he receive corticoprophylaxis according to NASCIS II scale combined with high doses of gastro protective medicaments. Postoperatively patient stable with sufficient breathing, there was no need for respiratory support. After two weeks he was translocated to his town and after that he had a central origin high temperature during one month without positive haemoculture.



A



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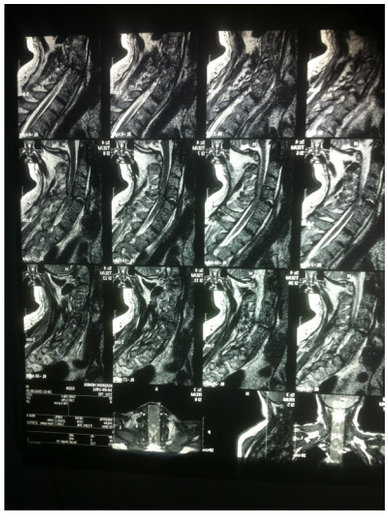

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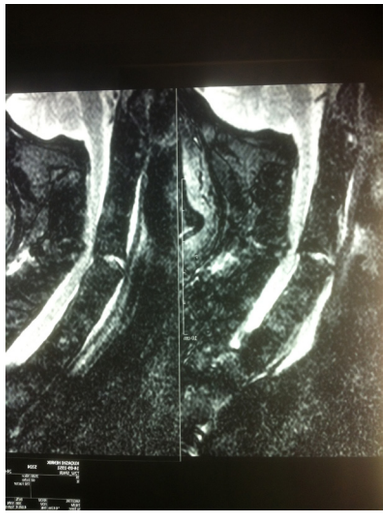

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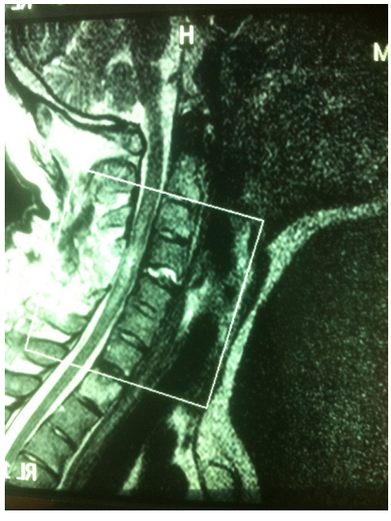

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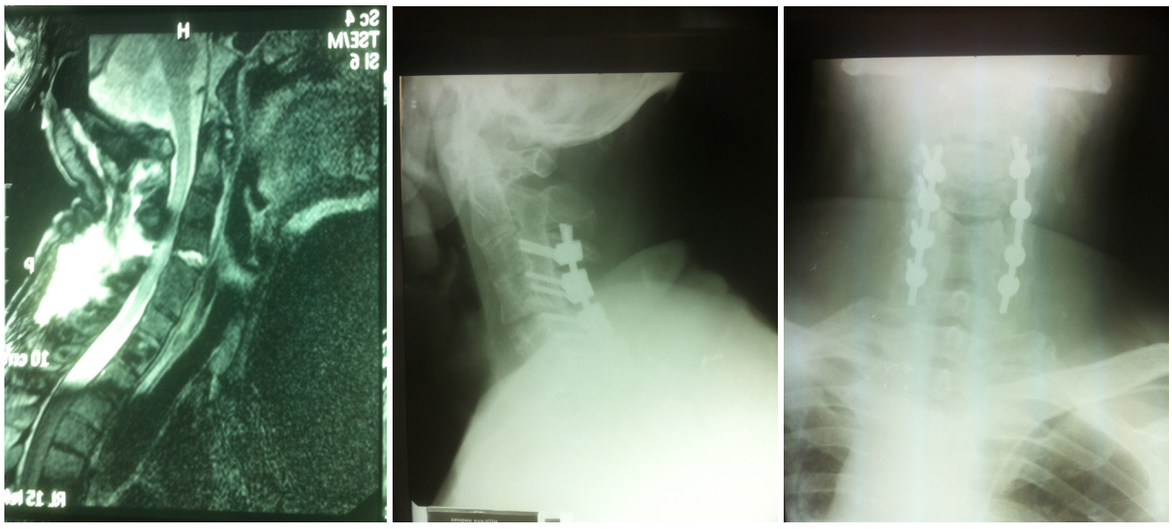

F G H

Xray: A, B - predoperative CT,

C, D, E, F - predoperative MRI

G, H - postoperative Xray

DISCUSSION

There are uncommon complications of spinal fractures with Ankylosing Spondylitis described in literature as aortic dissection, aortic pseudoaneurism, tracheal rupture and most of them finished lethally, or postoperative wound infection, deep venous thrombosis, pneumonia and respiratory insufficiently. Overall mortality in the post treatment phase described in literature was 6, 4%. (2)

Also there is difference between patients operatively treated and they have mortality 4, 9% in comparison with patients nonoperatively treated where mortality is 7, 9%.The most frequent cause of death in those patients was pneumonia and respiratory failure.

CONCLUSION

These patients with ankylosing spine have an increasing risk for fracture even after minor trauma.

Fractures of the ankylosed spine tend to be unstable, because ossified ligaments and surrounding tissue also fractured. An intrinsing unstable fracture configuration may lead to primary and secondary neurological deficit (1). The clinical outcome of patients fracturing their ankylosing spine is worse compared to the general spine trauma population,

Surgical treatment may be favorable for the patients with an ankylosing spine and spinal fracture, as this treatment option may be associated with lower complication and mortality rates and may lead to neurological improvement more frequently (11).

In such patients with ankylosant spondylitis – Bechterev disease and fracture of cervical spine we can recommend usually posterior approach because of the stiffness of the cervical spine and limited chances for performing the anterior approach. We can also recommend decompression combined with posterior fixation. Anesthesiologists have to use flexible canilla for intubation. Chances for neurological recovery are bigger if the decompression is immediately done.

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Case report

THE ACUTE SCROTAL PAIN: EPIDIDYMO-ORCHITIS VS. TORSIO TESTIS – A DIAGNOSTIC DILEMMA?

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ABSTRACT

One of the most common differentials for the acute scrotum is an epididymo-orchitis (EO), which can mimic the presentation of testicular torsion. Accurate diagnosis and differentiation of acute epididymo-orchitis from torsio testis (TT) is essential because TT is treated surgically and epididymitis with or without orchitis is treated medically. Distinguishing epididymoorchitis from TT is generally a clinical dilemma. Sonography remains the best imaging modality for these entities, but the sonographic findings can be complex and can mimic complicated epididymo-orchitis when dealing with partial TT. This case report illustrates the complex sonography findings. We present a case of a 24-year young man, a football player, presented to the Emergency department with a 4-day delayed history of progressive right testicular pain. A Color Doppler ultrasound was done which revealed diffusely increased blood flow in the right epididymis and Spectral Doppler evaluation showed areas of absent and reversed diastolic flow within the right testis. Differential diagnosis based on the sonographic features was severe complicated EO versus partial and intermittent testicular torsion. The patient refused surgical treatment - scrotal exploration and continued with antibiotics. On the next visit after 16 days, Color Doppler Doppler imaging showed a total abscense of blood flow of the right testis. Finaly, he accept surgical treatment and orchiectomy of the right testis was performed. Pathohistological findings determined a hemorrhagic testicular infarction. In doubtful cases our opinion is, better to perform surgical treatment – exploration than to treat with medications.

Key words: epididymo-orchitis, torsio testis, color Doppler ultrasound, hemorrhagic testicular infarction.

Introduction

Scrotal pain is a common complaint in a urological practice. Its diagnosis can prove challenging in both acute and chronic forms and requires a thorough and complete history and physical examination (1). The 4 most common causes of acute scrotal pain are trauma, testicular torsion, torsion of a testicular appendage, and epididymitis. Although all can appear clinically similar, subtle features in the history and physical examination may lead the examiner to the correct diagnosis (2). In approximately two thirds of patients, history and physical examination are sufficient to make an accurate diagnosis. Advances in imaging technology have served to decrease the number of individuals with acute scrotal pain requiring surgery. Only 14% to 38% of young men and boys with an acute scrotum have testicular torsion, despite history and physical findings indicating the need for emergent surgery. Thus, with potentially two thirds of all surgical explorations for acute scrotal pain being unnecessary, surgeons and radiologists have searched

for a reliable imaging technique. Recent studies have shown that, although neither 100% sensitive nor 100% specific, color Doppler ultrasound can be used effectively in the evaluation of acute scrotal pain (1). The acute scrotum can provide many diagnostic challenges to the Emergency Room Physician, Radiologist and Urologist. To compound the diagnostic dilemma, pathologies such as testicular torsion are time sensitive with a delay in diagnosis being potentially catastrophic to the young male. One of the commonest differentials for the acute scrotum is an epididymo-orchitis (EO), which can mimic the presentation of testicular torsion (TT). This infectious pathology is often managed as an outpatient with good results; rarely requiring surgical intervention. Testicular infections are usually treated with enteral or parenteral antibiotics, with little to no morbidity, it must be borne in mind that the progression to further complications can occur leading to greater morbidity and testicular loss. Few case reports and case series have been written highlighting acute testicular infarcts progressing from routine epididymal and testicular infections. (3).In this report, we present a case of a young male who delayed his visiting in the beginning of appearance of the simptomatology, who had most likely epididymo-orchitis which advanced to testicular torsion, which was not diagnosed at the time of presentation. We would also like to highlight the importance of clinical diagnosis and early referral in such cases.

Case report

We present a case of a 24-year young man , football player, presented to the Emergency department with a 4-day delayed history of right testicular pain. He indicated he had experienced sudden sharp pain in right testicle and enlargement of the testicle when he woke up on the second day. He explained that the pain was severe from the beginning and he was not feeling well even he started with ciprofloxacin 500 mg twice a day per os; patient exhibited no fever or penile discharge. The right testicle was moderately swollen and tender (approximately 6 cm in diameter), erythematous, and tender to palpation; Prehn's sign was negative (when elevation does not decrease the pain in the affected testicle –is positive), during inspection a high-riding and horizontally positioned testis (Brunzel's sign), no abnormally shaped masses fixed on testicle, low grade fever, and leukocytosis with a white blood cell count of 18,2. He reported similar episode one year before, but he passed it well with anibiotics (Figure 1).

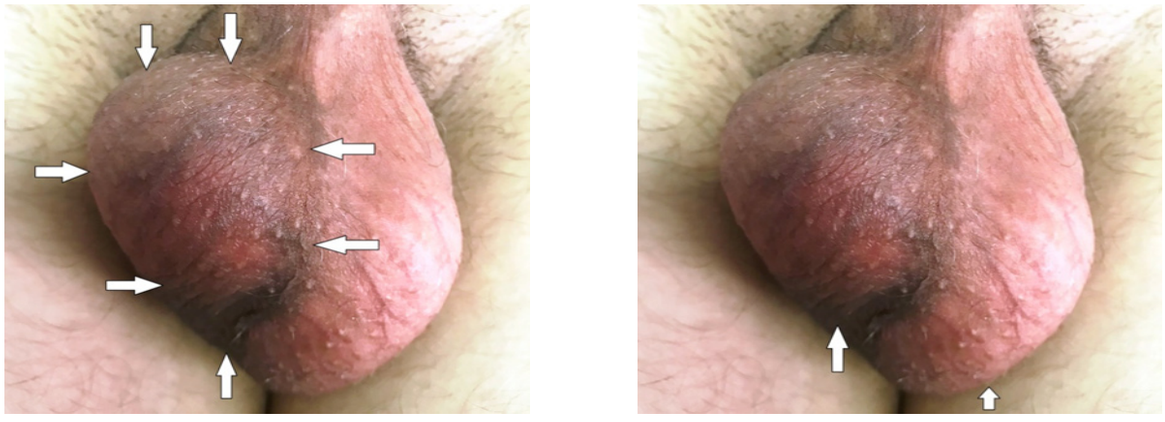

Figure 1. A high-riding and horizontally positioned right testis On the 4 day from beginning of the pain.

A clinical diagnosis of EO was again made, however, scrotal sonography was ordered on the same day to exclude TT. In mean time urino culture was sterile, analysed 2 days before. Scrotal sonography was performed utilizing a Mindray DC-N3 ultrasound system with a 10 MHz linear transducer. Color Power Doppler imaging and Spectral Doppler velocity measurements were done in addition to gray-scale imaging. Color Power Doppler imaging showed slightly increased blood flow in the right testis, diffusely increased blood flow in the right epididymis and normal blood flow in the left testis. Spectral Doppler evaluation showed areas of absent and reversed diastolic flow were noted within the right testis and a normal low resistance arterial flow waveform in the left testis. Differential diagnosis based on the sonographic features was severe complicated EO versus partial and intermittent testicular torsion (Figure 2). We conclude and we indicated surgical treatment – scrotal exploration. But, the patient and his mother refused.

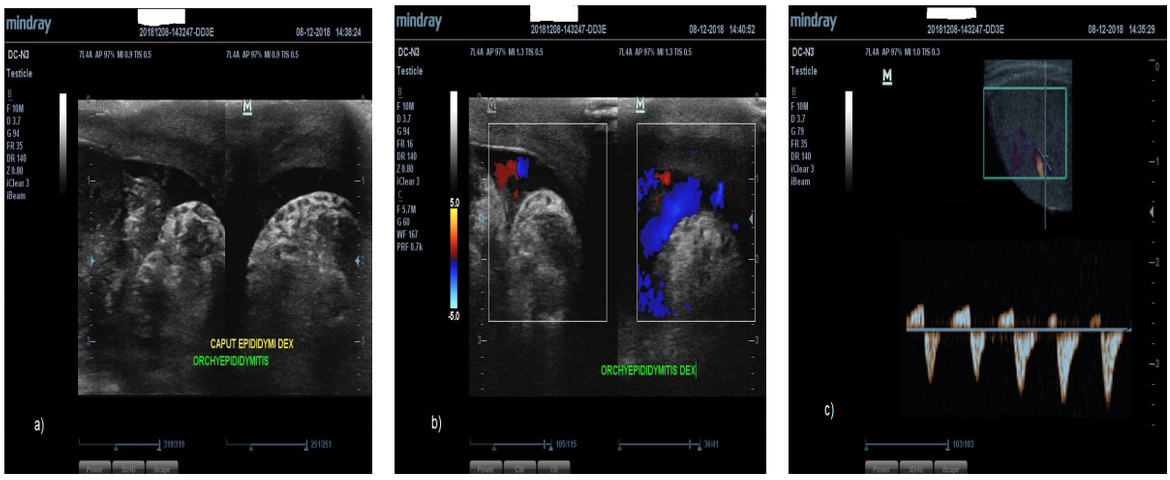

Figure 2. a) Ultrsanonography of the right testis demonstrates an edema of the right epididymis; b) Color Power Doppler shows slightly increased blood flow in the right testis; c) Spectral Doppler demonstrates a reversal of diastolic flow.

He continued with antibiotics and analgetics for ongoing 10 days. On the next visit after 16 days, Color Doppler imaging showed a total abscense of blood flow of the right testis. They decided and wanted to make more detailed and sophisticated imaging of the testicles such as Computed Tomography of the testicles. The result of CT of testicles was that the right epididymis and testis is morphologicaly changed with suspected epididymo-orchitis or torsio testis (Figure 3).

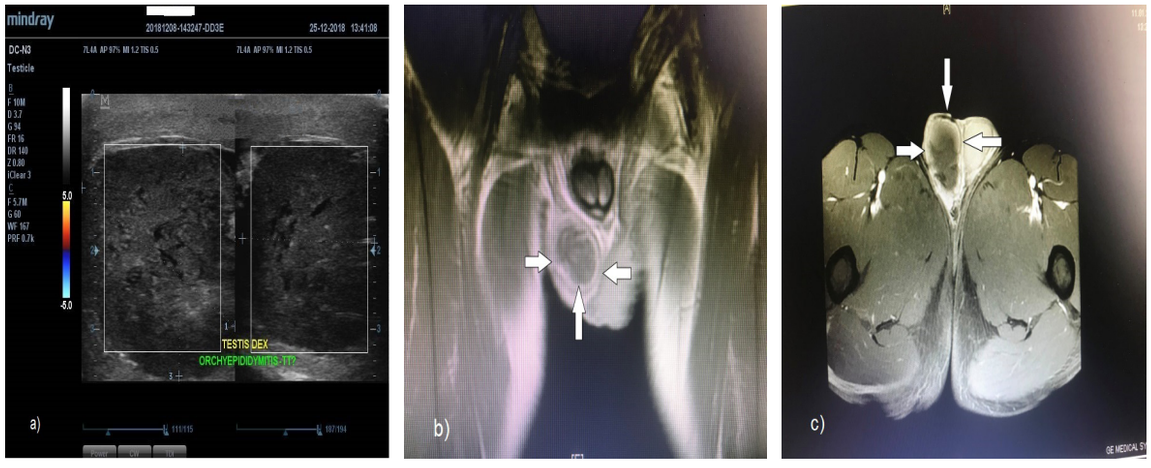

Figure 3. a) Power Doppler of the right testis demonstrates absence of complete blood flow in the right testis; b) and c) CT of the testicles

Finaly, they were persuaded and accept surgical treatment. We perfomed inguinal approach for better exploration. We found twisted spermatic cord once around his axis. After the incision of the tesis we saw haemathoma. Unfortunately, the final result was orchiectomy of the right testis. The material was send for pathohistological findings with final result of hemorrhagic testicular infarction. Figure 4.

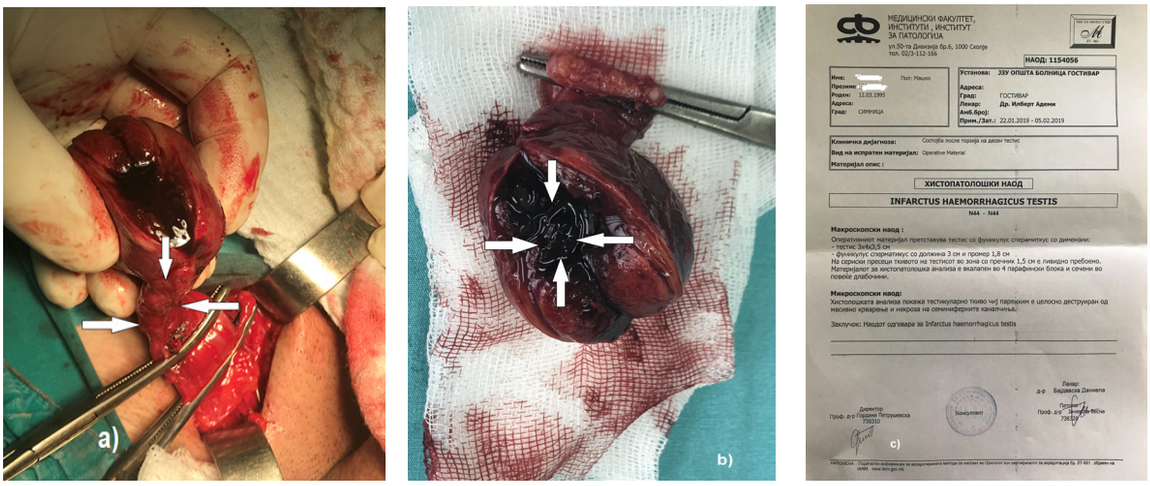

Figure 4. a) twisted spermatic cord; b) Incision of the testis- haemathoma; c) HP result

DISCUSSION

Epididymitis is common cause of acute scrotal pain that must be differentiated from the more severe testicular torsion. According to the Centers for Disease Control and Prevention's ambulatory health care data, epididymitis accounted for 1 in 144 outpatient visits in 2002 in the United States in men aged 18 to 50 years (4). Epididymitis, unlike testicular torsion, presents with gradually increasing dull, unilateral scrotal pain. Involvement of the vasa may result in exquisite pain that affects the entire hemiscrotum as well as the spermatic cord. Discerning epididymitis from torsion may be difficult; however, a history of prior genitourinary tract procedures and sexual activity are more suggestive of epididymitis (5). On physical examination, a tender and swollen epididymis and normal cremasteric reflex is observed. Urinalysis, urine cultures, and urethral cultures must be performed to identify possible causative agents. A positive urinalysis and urine cultures, along with elevated white blood cell count, favor a diagnosis of epididymitis but do not exclude torsion. Color Doppler ultrasound or nuclear scintigraphy to assess blood flow to the scrotum and its contents will help to differentiate between the two entities. Doppler ultrasound would show increased blood flow, because this is an inflammatory condition. Complicated epididymo-orchitis may result in testicular infarction. Infection of the epididymis or testicle can result in marked swelling and edema of the spermatic cord that may impede testicular blood supply, in the absence of testicular torsion (5). Empiric antibiotic treatment should be started if the clinical suspicion is high. Epididymo-orchitis should be treated with antibiotics if the urine analysis or urine culture suggests bacterial etiology (6-7). Surgery is an option for patients with genitourinary abnormalities (8).

Testicular torsion is a medical emergency, requiring prompt treatment or risking the loss of the testicle. The incidence is 1 in 4,000 males under the age of 25 years (9). It may be intravaginal or extravaginal and is typically seen in neonatal patients and in adolescents prior to complete testicular descent and scrotal wall fusion. Intravaginal torsion occurs when the testicle can freely rotate within the tunica vaginalis; this can be due to a congenital anomaly called the bell clapper deformity. This deformity is due to failure of posterior anchorage of the gubernaculum, epididymis, and testis, thus allowing the testis to freely rotate within the tunica vaginalis. Extravaginal torsion occurs when the testis rotates within the scrotum owing to inadequate fusion of the testicle to the scrotal wall or increased mobility (9-10). The pathogenesis of a testicular infarct due to EO is poorly understood. In the event when it occurs a number of factors are postulated to contribute: inflammatory infiltration causing compression of the spermatic cord, thrombosis secondary to venous congestion and bacterial exotoxins are all thought to play a role (11). The torsion follows rotation of the spermatic cord and results in ischemia. The degree of testicular torsion is directly correlated with the possibility of salvage after torsion and time to necrosis. The classic presentation of testicular torsion is acuteonset, intense, unilateral scrotal pain. Patients may also complain of nausea and vomiting, likely secondary to pain (12). Intensity increases owing to edema and resultant capsular stretching (13). Patients may also have a history of scrotal pain that may be related

to prior ischemic episodes that resolved spontaneously. On examination, the hallmark of testicular torsion is a 'high riding' testis due to shortening of the cord. Additionally, the testis may have an abnormal (e.g., transverse) position in the scrotum (12). Absence of the cremasteric reflex is a characteristic of torsion in the pediatric population (14). A normal cremasteric reflex would result in elevation of the ipsilateral testis after an extra gentle stroke of the inner thigh. The cremasteric reflex is rarely seen in patients with testicular torsion. Labs and studies should include urinalysis and scrotal ultrasound to confirm the diagnosis. Urinalysis showing hematuria or leukocytosis is more typical of epididymo-orchitis than torsion. Doppler ultrasonography can be used to assess testicular blood flow, which is reduced or absent in testicular torsion. This technique, however, is highly operator dependent and may have significantly high false interpretations in young children or neonates with small vessels (15). Although torsion usually occurs around puberty and epididymitis typically affects sexually active men after the age of 20 years, age distribution may be clinically misleading and should not be relied upon for a diagnosis. Testicular torsion commonly presents with sudden onset of pain followed by nausea, vomiting, and absence of urinary symptoms. Physical examination shows a swollen and tender testis, an absent cremasteric reflex, and pain not relieved by elevation of the scrotum above the level of symphysis pubis (Prehn's sign) (16). Doppler ultrasonography is the first-line imaging modality used to triage patients with acute scrotal pathologies (17). When no detectable flow is seen in the testicle, the presumptive diagnosis of testicular torsion is made. Color flow Doppler alone has a sensitivity of 78.6%–89% and specificity of 77%– 100% for the diagnosis of testicular torsion (18). Testicular torsion must be identified and promptly manually or surgically reversed, as irreversible damage can begin as early as 6 h after the torsion event, with 50% of testes salvageable after 12 h, and 10% salvageable after 24 h (16).

However, generally urologist duty is to provide the protocol: the clear history (time and the manner of pain appearance), accurately physical examination, and color Doppler ultrasound as a most important procedure. In doubtful cases our opinion is, better to perform surgical treatment – exploration than to treat with medications.

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Case report

A SERIES OF CASES WITH PERM IN ASSOCIATION WITH GAD, NMDA, LGI1 AND OTHER ANTIBODIES

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ABSTRACT

Objectives of research: Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a severe syndrome that presents with autonomic features, hyperekplexia, painful spasms and breathing problems. It is part of the spectrum of the stiff-person syndrome (SPS) with anti-glutamic acid decarboxylase (GAD) antibodies in up to 80% of patients.

Methods: We present a series of 3 cases in The Republic of North Macedonia that were diagnosed as Progressive Encephalomyelitis with rigidity and myoclonus.

Results: A series of 3 cases have been processed, which are diagnosed as Progressive encephalomyelitis with rigidity and myoclonus (PERM). The initial symptoms of the patients were bilateral ataxia, dysarthria, the change of sensations in the area of the feet, moments of forgetting things, unstable posture followed by the involuntary movement of the lower limbs, shaking of the upper limbs. The goal is to show the association of the presence of certain antibodies to the progressive clinical manifestations of the disease itself. Furthermore, all patients were GAD, Hu D and Ri positive. Two were positive for the NMDA antibodies. Only one patient was positive for Anti-CMV, EBV Viral Capsid Antigen-Antibody (VCA) IgG, Anti Herpesvirus VZV IgG, anti-LGI1 antibodies. It is common that all three patients have been given/given series of plasmapheresis and IVIG cycles, but without any significant progress. Unfortunately, one ended up lethal, and the other two are not in an enviable state.

Conclusions: These three cases do not only show the clinical spectrum of PERM, but also the association of this disease with Hu, Ri, GAD, NMDA and LGI1, and other antibodies. This combination of antibodies may be responsible for the progressive character of this disease.

Keywords: PERM, GAD antibodies, NMDA antibodies, IVIG

INTRODUCTION

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a severe syndrome that presents with autonomic features, hyperekplexia (brainstem myoclonus or excessive startle), painful spasms and breathing problems [1]. This syndrome can present with an insidious onset, as well as an acute or subacute presentation, or exacerbations on a chronic course [2]. Symptoms can be explained by the disruption of the inhibitory glycinergic synaptic transmission, which is prominent in the spinal cord and brainstem [1]. Classical PERM affects women two to three times more often than men. Several classifications have been proposed for SPS according to the severity or distribution of the stiffness, related neurological findings and association with neoplasia [3]. Immunomodulation using corticosteroids, intravenous (IV) immunoglobulin, plasma exchange or cyclophosphamide are described as an effective treatment [4]. Initial diagnosis of PERM is not easy and literature is limited regarding the long-term course of the syndrome.

Here, we report a clinical presentation of PERM in three different patients, with more common moments.

METHODS & MATERIAL

We present a series of 3 cases in The Republic of North Macedonia that were diagnosed as Progressive Encephalomyelitis with rigidity and myoclonus (PERM).

RESULTS

(Case1)

A 49-year-old man was referred to the State Hospital of Neurology in Skopje for bilateral ataxia, changing of sensations in the area of his feet and moments of forgetting things. The difficulties started two months before the reception of the Neurology Clinic. A few days after he was admitted to the hospital, the patient had complete incapability for movement and paralysis of the lower limbs. Meanwhile, deterioration of speech with occasional attacks of confusion and loss of control of urination followed. In addition to this, the surface sensation and deep sensibility for vibrations of the upper and lower limb were lost. The findings from the cerebrospinal fluid tests were in favor of hematoencephalic barrier dysfunction. Also, the EEG examination was dominated by low-voltage, slow wavy activity from theta rank. SEP of n. medianus and n.tibialis showed cortical responses with prolonged latency, bilaterally. This finding is in favor of a defect in the conduction of the central and peripheral paths bilaterally. Moreover, the finding of the magnetic resonance showed that on the level of the foramen magnum, there were punctiform, hypersignal lesions peripherally with restriction of diffusion. Cerebellar, bilateral hyper signal lacunar lesions were found bilaterally. Global, cortical atrophic events also, were observed both frontally and temporally. Besides, small pleural effusions were observed on the chest Echo. Diabetes Mellitus was diagnosed 10 years ago. Therefore, the differential diagnostic was thought to be diabetic polyneuropathy. He was positive to GAD (glutamate decarbox.) and NMDA (N-methyl-D-aspartate) antibodies. The patient had received 1 cycle of IVIG, 2g/kg TT, but without therapeutic effect. Unfortunately, the patient died.

(Case2)

A 38-year-old woman, previously healthy was referred to the State Hospital of Neurology in Skopje for the subacute onset of severe and progressive gait disturbance associated with painful muscular rigidity and spasms of the trunk and lower limbs. Additionally, unstable posture followed by involuntary movement of the right leg appeared. After a short period, there was also the involuntary movement of the left leg with propagation to myoclonic limb jerks with hyperekplexia. Symptoms appeared 4 months before hospitalization with a blurred vision of the left half of the eye field and in few times seizures described like GTCS, but without urination and biting of the tongue. EEG showed theta-delta dysrhythmia, the evoked potential was normal, except SEP of n. tibialis with mildly prolonged latency. Manganese was slightly higher at 1.3 (rr 0.3-1.1), GAD (glutamate decarbox.) antibodies were 33.6 (rr<10) and she was also positive to Hu D and Ri antibodies. Symptoms were partially responsive to baclofen, corticosteroids, and levetiracetam. The patient so far has received 3 cycles of IVIG, and recently a series of a 3 plasmapheresis, but without a marked therapeutic effect.

(Case3)

A 40-year-old man was referred to the State Hospital of Neurology in Skopje because of a condition that previously persisted for a month. Actually, the patient was in a coma, with a characteristic position. Hands were in flexion in the elbows, the palms were in fists. Occasionally there was a shaking of the upper limbs. In addition to this, he had visual hallucinations and did not respond to verbal stimuli. On mechanical irritation, he responded by shaking the upper extremities in the form of myoclonus. The pupils were tightened. The left nasolabial ditch was lowered. In the urine, blood was noticed. Furthermore, cortical reductive changes of diffuse character were detected on the computerized tomography of the head. On the other hand, decreased values of cortisol and ACTH were detected. The performed gas analyzes showed hyposaturation, hypoxemia, and hypocapnia. There was a metabolic acidosis which was compensated by respiratory alkalosis. Meanwhile, the magnetic resonance of the brain showed hypersignal changes at the basal ganglion level, as well as, on the nucleus caudatus. Anti-CMV, EBV Viral Capsid Antigen-Antibody (VCA) IgG, Anti Herpesvirus VZV IgG, anti-LGI1 antibodies, were all positive. He was also positive to GAD (glutamate decarbox.) and NMDA (N-methyl-D-aspartate) antibodies. Myoclonic attacks were registered on multiple occasions. The patient received 3 cycles of IVIG and 3 plasmaphereses, but no

improvement was observed on the neurological and somatic plan.

DISCUSSION

A major breakthrough in our understanding of the pathogenesis of PERM occurred in 1988, when an association between anti-GAD antibodies and PERM was first reported by Solimena et al. 26-GAD is the rate-limiting step in the decarboxylation of L-glutamate to ε-aminobutyric acid (GABA) [5]. Anti-GAD antibodies are 80% positive in patients with PERM. Other antibodies, such as N-methyl-D-aspartate (NMDA) receptor antibodies are associated with the different sub units of the NMDA receptor. Antibodies to the delta or NR2 subunits of the NMDA receptor are associated with limbic encephalitis, systemic lupus erythematosus (SLE), ataxia and epilepsia partialis continua. Antibodies against the NR1, NR2A, and NR2B subunits of the NMDA are found in patients presenting with psychiatric symptoms, amnesia, seizures, dyskinesias, autonomic dysfunction and loss of consciousness [6]. Autonomic instability is a common feature in adults, with about half of patients developing central hypoventilation that generally requires weeks of mechanical support [7]. Most patients have abnormal CSF studies with a lymphocytic pleocytosis. At presentation, about half of the patients have abnormal MRI findings, most commonly increased signal on fluid-attenuated inversion recovery (FLAIR) or T2 sequences in the cerebral or cerebellar cortex or medial temporal lobes. Abnormalities have been reported in other areas, such as the corpus callosum or brainstem [8]. Just over half of patients have an associated tumor, most commonly an ovarian teratoma that can be mistaken for a benign cyst. The detection of a tumor is rare in male patients. Other tumor types in isolated cases include teratoma of the mediastinum, small-cell lung cancer (SCLC), Hodgkin's lymphoma, neuroblastoma, breast cancer, and germ-cell tumor of the testes [9]. Very interesting, anti-LGI1 antibodies is manifesting with memory deterioration, epileptic seizures, mental disorders, and hyponatremia. The hyponatremia is a characteristic feature of anti-LGI1 AE, and 60%~ 88% of such patients have refractory hyponatremia according to the prior studies. The pathogenic mechanism is likely associated with the syndrome of inappropriate antidiuretic hormone secretion causing by the simultaneous LGI1 expression of the hypothalamus and kidney. Our case was consistent with prior reports, with a lower blood level of sodium (119.1 mmol / l) [10]. To sum up, the diagnosis of PERM is difficult to set. EMG, antibodies in serum and CSF could help to confirm the diagnosis. Initial clinical presentation can be very unspecific and uncommon, and this case is no exception. A high level of D-dimers was observed in the three patients. This explains the existing risk of thromboembolism. Meanwhile, common differential diagnoses of PERM syndrome are stiff person syndrome, paraneoplastic SPS and NMS [11]. With respect to immunotherapy, plasmapheresis, intravenous immunoglobulin (IVIG), corticosteroids and rituximab have been reported to be successful in individual cases, although the efficacy of these agents has not been established. In addition, some reports have demonstrated the efficacy of long-term basement azathioprine treatment for SPS spectrum disorders. However, PERM remains an expanding clinical entity that is constantly being enriched with new symptoms and antibodies [12]

CS-corticosteroids, CYS-cyclosporine, GAD-Ab-sglutamicaciddecarboxylase antibodies IVIg intravenous immunoglobulin, PE-plasmapheresis, PERM-progressive encephalomyelitis with rigidity and myoclonus

These three cases do not only show the clinical spectrum of PERM, but also the association of this disease with Hu, Ri, GAD, NMDA and LGI1 antibodies. This combination of antibodies may be responsible for the progressive character of this disease. The plasmapheresis and IVIG cycles did not show significant therapeutic progress. Unfortunately, one of them ended up lethal, and the other two are in a bad sta te..

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Table 1 Summary of clinical features, laboratory findings, and outcome

Patient no.	Case 1	Case 2	Case 3
Age at onset/sex	49/M	38/F	40/M
Diagnosis	Idiopathic PERM	Idiopathic PERM	Idiopathic PERM
Initial symptoms	Bilateral ataxia, changing of sensations in the area of the feet and moments of forgetting things	Unstable posture followed by involuntary movement of the right leg	Shaking of the upper limbs, ataxia, dizartrija
Ocular movements	Horizontal gaze palsy, gaze-evoked nystagmus	Blurred vision of the left half of the eye field	Narrowed pupils
Myoclonus	Moderate	Moderate	Strong
Hyperreflexia	Moderate	Moderate	Moderate
Hyperekplexia	Mild	Moderate	Moderate
Rigidity, spasm, stiffness	Strong	Strong	Strong
Other features	Diabetes mellitus type 2, Diabetic polyneuropathy Hyperlipidemia	Seizures, hypothyroidism	Visual hallucinations Coma
MRI	On the level of the foramen magnum, there were nctiform, hypersignal lesions peripherally with restriction of diffusion.	Complete obliteration of the front subarachnoid space with mild compression on the medulla spinalis	Hypersignal changes at the basal ganglions level, as well as, on the nucleus caudatus
GAD-Abs titer (IU/ml)	32.7	33.6	33.1
Other Abs	Hu D and Ri antibodies, NMDA antibodies	Hu D and Ri antibodies	NMDA antibodies Hu D and Ri antibodies Anti-CMV EBV Viral Capsid Antigen-Antibody (VCA) IgG Anti Herpesvirus VZV IgG Anti-LGI1 antibodies
Treatment	CS CYS 1 cycle of IVIg	3 cycles of IVIg, CS, CYS 3 series of PE	3 cycles of IVIg, CS, CYS 3 series of PE
Outcome (observation periods)	Without therapeutic effect. The patient died.	Initially improved with consecutive relapse.	No improvement was observed on the neurological and somatic plan.

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Case report

ПРИКАЗ НА СЛУЧАЈ (MYCOSIS FUNGOIDES),ХИПО-ХИПЕР ПИГМЕНТИРАН ТИП

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АПСТРАКТ

Mycosis fungoides е најчеста варијанта на кутаните Т-клеточни лимфоми и е типичен кај повозрасната популација. Во повеќето случаи е индолентен со спора еволуција од макулозна кон плакарна, на крајот со туморски промени на кожата. Во подоцнежните стадиуми со зафаќање на лимфните јазли и висцерализација.

Даваме приказ на случај со ретка форма на хипо – хиперпигментиран Mycosis fungoides кај млада пациентка на 26 годишна возраст. Хистопатолошки верифициран, направени две биопсии, дијагнозата е потврдена и со имунохистохемија. Спрема ревидираната класификација за стејџинг (ISCLE/EORTC 2007) пациентката е во IB стадиум.

Применета терапија кај пациентката PUVA (Psoralen +UVA) 35 сесии. На последната контрола во септември 2015 без знаци за прогресија на болеста.

Клучни зборови: Mycosis fungoides, хипо – хиперпигментиран

ВОВЕД

Терминот кожен Т-клеточен лимфом(CLTC) опфаќа група различни лимфоматозни неоплазми на хелперните Т клетки кои се презентираат во кожата,но подоцна може да ги зафатат лимфните јазли,периферните крвни клетки и органите.Примери за (CTCL) се Mycosis fungoides,Sezary Sy и лимфом на кожата.Малигните клетки имаат значителна склност кон кожата особено епидермисот,кога клетките почнуваат да ја губат склоност кон епидермисот заболувањето почнува да напредува кон системско заболување.

MYCOSIS FUNGOIDES

Дефиниција

Mycosis fungoides е за прв пат опишан во 1806 од Аliберт како печурка-лајк неоплазија на кожата.(1)

Mycosis fungoides (МФ) е кутан Т клеточен лимфом,со спора прогресија и непозната етиологија.Има спора

прогресија со појава на плаки на почетокот,нетретиран еволуира во нодули и ,но во подоцнежните стадиуми може да ги зафати лимфните јазли и внатрешните органи и да добие фатален тек.Лимфоидните инфилтрирачки клетки,покажуваат имунолошки карактеристики на Т-хелпери,а болеста може да прогредира со години.(2,3)Типичните за Микозис фунгоидес се мали до средно големи лимфоцити со цереброзиформи нуклеуси.

Најчесто се јавува после 40 години , со лесна предоминација на машкиот пол и црната раса.

Патогенеза

Причините за појава на (МФ) се непознати ,кај помал број од болните изолиран е ретровирус и најдени се ретровирусни антитела во серумот.Карциноидите од околината исто така би можеле да бидат причинители. (4,7)

Клиничка слика

МФ може да се манифестира во различни клинички форми

А) Albert Bazin (класичен тип)

- Премикотичен стадиум (печ стадиум)

- Инфилтративен стадиум (плакарен стадиум)

- Стадиум на тумор

Б) Mycosis fungoides D'emblee

- (Vidal i Broq)

В) Еритродермична форма

- (Hallopeau I Besnier 1891)

Во плакарниот и туморскиот стадиум често е присатна палпабилна лимфаденопатија,тие се одраз на дермопатска лимфаденопатија,со прогресија на болеста и во лимфните јазли се јавуваат карактеристики на Т- клеточен лимфом. Висцерално зафаќање може да се појави во подоцнежните фази најчесто се афицирани белите дробови,лиенот,хепар от,бубрезите но може да биде зафатен секој орган.(5)

Патохистологија

Доколку постои сомневање за МФ треба да се земат биопсии од овеќе кожни лезии.Најзначајно случување кое овозможува дистинкција на МФ од другите кутани лимфоми е епидермотропизмот,односно инфилтрација на епидермот со лимфоцити.Оваа инфилтрација се состои од атипични клетки,кои често формираат остро дефинирани гнезда опкружени со хало(Pautrier-ови микроапсцеси).(6)Постои минимална спонгиоза,поради тоа е тешка диференцијацијата од другите спонгиформни дерматити.

Во премикотичниот стадиум патохистологијата покажува неспецифичен дерматитис,но може да се детектира линеарна субепидермална инфилтрација со малку атипични клетки,минимална егзоцитоза,хистиоцити во инфитратот.

Во инфилтративниот стадиум епидермисот покажува акантоза,хиперкератоза и паракератоза,како и патогномичните Потрие-ови микроаппсцеси налик на апсцес агрегации на атипични лимфоидни клеетки во епидермисот,широка ,тракаста инфилтрација под епидермисот.Клеточниот инфилтрат во наредните стадиуми покажува изразена атипија и полиморфност. (7)

Дијагноза и диференцијална дијагноза

1.Анамнеза и дерматолошки статус

2.Хистопатологија

3.Лабараториски тестови (крвна слика,функционални тестови за бубрези и хепар,мокрачна киселина)

4.Испитување на коскена срцевина(стернална пункција или биопсија од лијачен гребен

5.Имунолошки испитувања(Т-лимфоцити,Б-лимфоцити со потклассите,електрофоеза)

6.Радиолошка егзаминација(граден кош,и.в. пиелографија,ехо,радиоизотоски испиувања,КТ)

7.Лимфангиографија

8.Имунохистохемија

ДД

Нумуларен екцем,псоријаза,лихенифициран егзем.

Тек на болеста

Премикотичниот стадиум може да трае нколку години,болеста е споро прогресивна.Прогнозата е неповолна доколку постојат тумори,зафаќање на лимфни јазли и органи.

Терапија

Терпискиоот пристап зависи од тоа во кој стадиум се наога болеста (8).

ТАБЕЛАРЕН ПРИКАЗ НА ТЕРАПИЈА ПО СТАДИУМИ

Table 7

Treatment Recommendations for Mycosis Fungoides by Stage

Diagnosis/Stage	Initial Treatment	Treatment for Relapsed or Refractory Disease
Unilesional patch T1, N0, M0 (stage IA)	Localized, superficial radiotherapy Topical carmustine Topical mechlorethamine Topical corticosteroids PUVA UVB	Same as initial treatment
Limited patch/plaque T1, N0–1M0 (stage IA)	Localized, superficial radiotherapy Topical carmustine Topical mechlorethamine PUVA UVB (only for patches) Topical bexarotene	Same as initial treatment TSEBT Topical or oral bexarotene Interferon-α alone PUVA + interferon-α Topical corticosteroids
Extensive patch-plaque (symptoms controlled, minimal plaque thickness) T2, N0–1M0 (stage IA, IIA)	Topical mechlorethamine Topical carmustine PUVA ± interferon-α UVB (only for patches) TSEBT + adjuvant PUVA or HN2	Same as initial treatment TSEBT Topical or oral bexarotene Interferon-α alone Topical corticosteroids
Extensive patch-plaque (symptoms uncontrolled, indurated plaques) T2, N0–1M0 (stage IB, IIA)	TSEBT + adjuvant PUVA or mechlorethamine	Topical mechlorethamine Topical carmustine PUVA + interferon-α Topical corticosteroids Repeat TSEBT
Cutaneous tumors T3, N0–1M0 (stage IIB)	TSEBT + adjuvant mechlorethamine or photophoresis Interferon-α alone Oral bexarotene Denileukin diftitox Combination therapy	Topical mechlorethamine + local radiotherapy Oral bexarotene Denileukin diftitox Systemic chemotherapy Repeat TSEBT
Erytheroderma T4, N0–1M0 (stage III)	TSEBT + adjuvant photophoresis PUVA + interferon-α Photophoresis alone	Methotrexate Oral bexarotene Denileukin difititox Gemcitabine Fludarabine ± interferon-α Pentostatin ± interferon-α 2-chlorodeoxyadenosine Repeat TSEBT Allogeneic transplant
Nodal or visceral disease (stage IV)	Clinical trial Allogeneic transplant Methotrexate TSEBT Topical mechlorethamine Topical carmustine PUVA + interferon-α Topical corticosteroids Localized, superficial radiotherapy	Same as initial treatment Systemic chemotherapy as listed above
Transformed to large cell variant	Same as stage IV Consider rituximab if CD20+ Trimetrexate Allogeneic transplant	Same as stage IV

PUVA = Psoralen and ultraviolet A light therapy; TSEBT = total skin electron beam therapy; UVB = ultraviolet B light.

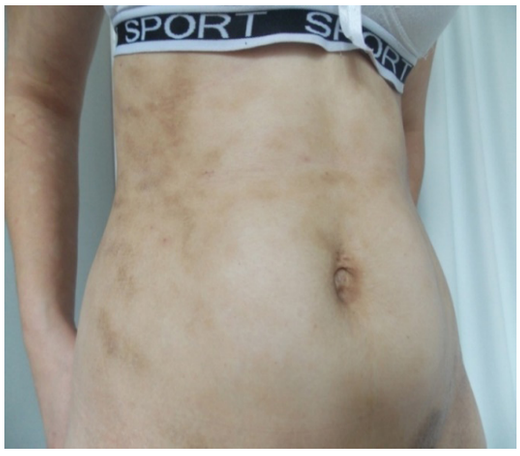
ПРИКАЗ НА СЛУЧАЈ

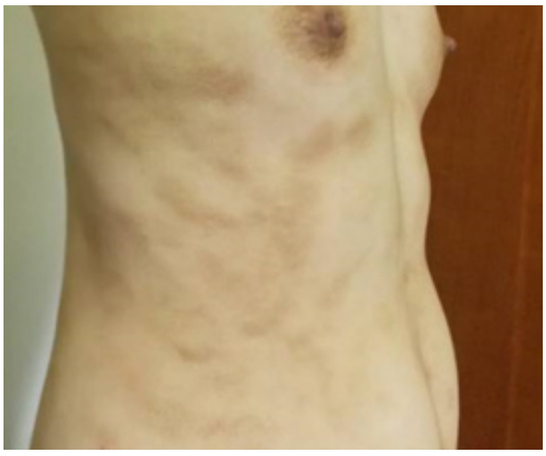
Пациентка на 26 годишна возраст,мажена ,мајка на две здрави деца.Не дава податок за претходна историја на заболувања како и негативна анамнеза за спектарот на атописки заболувања.Поради професионалната определба експонираност на пестициди и билки.

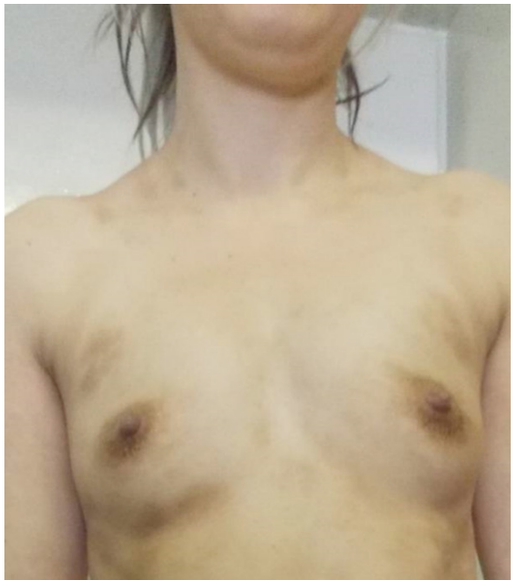
Сегашната болест започнува во 2013/2014 со појава на јадеж локализиран на екстремитетите во епизодични појавувања.Пациентката била водена под дијагноза (Eczema,Pruritus).

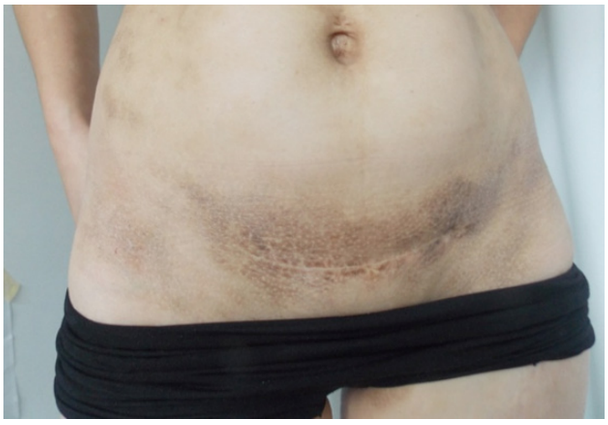
Дерматолошки статус

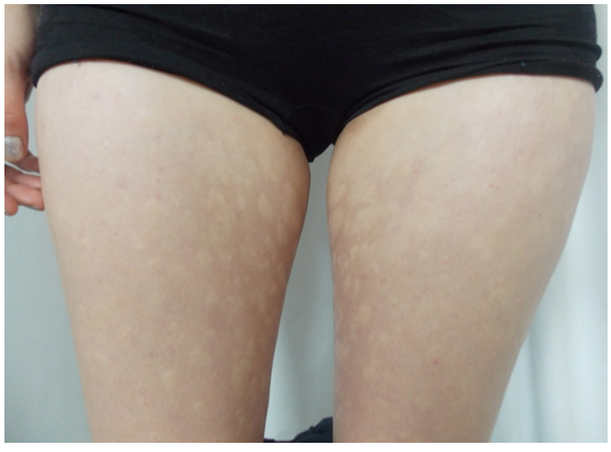
Фицпатрик тип 3 (кожен тип), на хипер и хипопигментирани плаки и острови на здрава кожа,дигитална дистрибуција,без еритем и десквамација. Во пределите на триење ,дразба гради и ингвинално присатен Кебнеров феномен..Од субјективните тегоби присатен изразен јадеж.











Спроведени дијагностички процедури

1.Земени две биопсии (прва од лесно инфилтрирана депигментирана плака-долен екстремитет,втора од лесно инфилтрирана пигментирана плака-абдоминална регија)

И двата хистопатолошки наоди патогномични за болеста МФ

2.Лабараториски испитувања на крв и функционални тестови –резултати во граници на референтни вредности.

3.Периверна крвна размаска –без атипични клетки

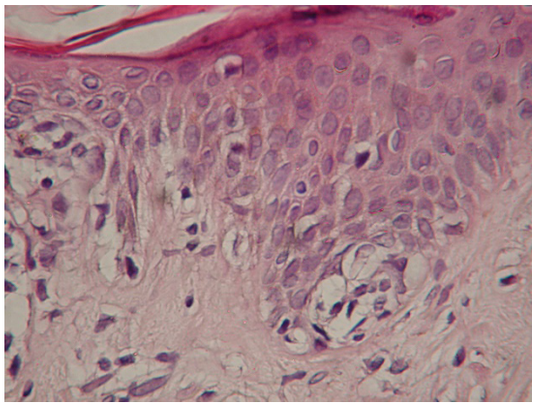
4.Егзаминација на коскена срцевина –уредни

5.Нема лимфаденопатија

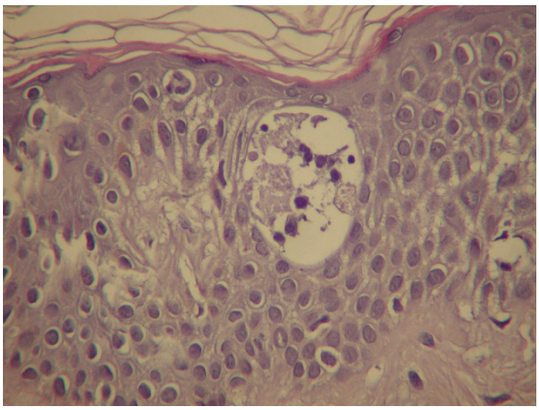
6.ЕХО на абдомен –уреден наод

7.РТГ пулмо-уреден наод

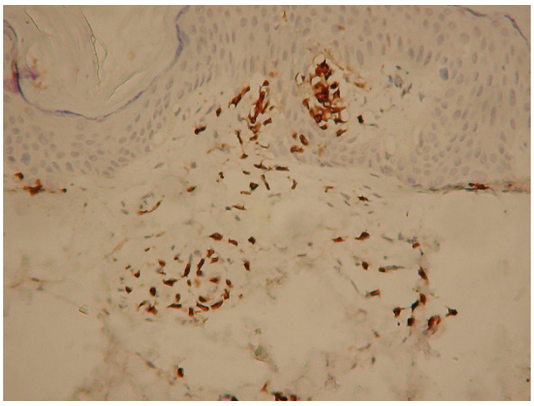
8.Имунохистохемија(изобилство на CD3+ Т клетки во епидермис,CD8T клетки во рамките на епидермис



1.Биопсија од хиопигментиран дел од на кожата,прикажува лумфоцитен инфилтрат, горниот дерм и епидермотропизам.(Х&Е)



2.Биопсија од хиперпигметиран дел кожата ,видливи Потриеови микро абцеси



3. CD 8 Т клетки во епидермисот

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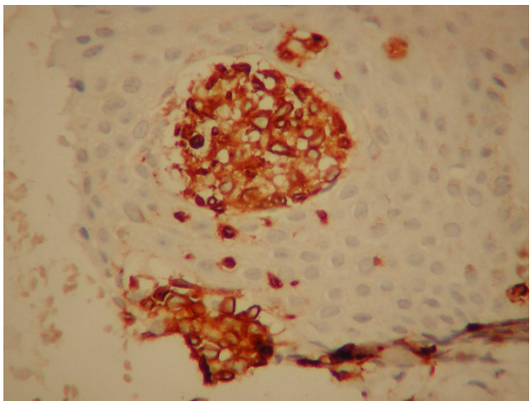

4. Имунохистохемиско испитување покажува изобилство CD 3+Т клетки во епидермис

ISCL/EORTC CLASSIFICATION AND STAGING (2007)

IB (T2, N0, M0, B0)

Skin		
T1	Limited patches and/or plaques covering < 10% of the skin surface T1a (patch only) vs T1b (plaque ± patch)	
T2	Patches or plaques covering ≥ 10% of the skin surface T2a (patch only) vs T2b (plaque ± patch)	
T3	One or more tumors (≥ 1-cm diameter)	
T4	Erythema covering ≥ 80% body surface area	
Node		
N0	No clinically abnormal peripheral lymph nodes	
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0–2 (a = clone negative / b = clone positive	
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3 (a = clone negative / b = clone positive)	
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 3–4 or NCI LN4 (a = clone negative / b = clone positive	
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation	
Visceral		
M0	No visceral organ involvement	
M1	Visceral involvement	
Blood		
B0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells	
B1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2	
B2	High blood tumor burden: ≥ 1000/μL Sézary cells with positive clone	

IA	T1	N0	M0	B0–1
IB	T2	N0	M0	B0–1
IIA	T1–2	N1–2	M0	B0–1
IIB	T3	N0–2	M0	B0–1
IIIA	T4	N0–2	M0	B0
IIIIB	T4	N0–2	M0	B1
IVA1	T1–4	N0–2	M0	B2
IVA2	T1–4	N3	M0	B0–2
IVB	T1–4	N0–3	M1	B0–2

ТЕРАПИЈА

Во периодот Мај/Јуни2015 ординирана терапија (PUVA-Psoralen +UVA) 35 експозиции,

Во период Јули /Август2015. (препорака за природна фототерпија).

Последна контрола Септември 2015 без прогресија на болеста,парцијална ремисија(подобдрување на хиперпигментациите,нема репигментација на депигментираните лезии,среден јадеж.

Препорачана тераппија локални кортикостероиди и емолиенти.

ДИСКУСИЈА

Она што го прави овој приказ на случај интересен е најпрво возраста на пациентката ,бидејќи во оваа возраст исклучително ретко се јавува оваа болест.И вториот момент кој што е поитригантен е клиничката слика на болеста со хипо-хиперпигментирани лезии. Во литературата опишани се 31 клиничко-патолошка варијанта на МФ ,каде што како посебни варијанти се опишани Хиперпигментиран и Хипопигментиран тип.

Хипопигментираниот тип(за првпат објавен1973,кај фототип 4-5,кај белата раса,почеста варијанта во помлада популација)

Хиперпигментиран тип(за првпат објавен 1987,кај фототип 4-5,претезно кај белата раса ,кај повозрасна популација)

Дали е нашиот случај нова варијанта од спектарот на МФ Дисхромика ?

Од дијагностички аспект клиничките варијанти имаат големо значење,за полесна и побрза дијагностика ,затоа што почетните стадиуми на МФ се тешки за дијагноза затоа што постои спектар од диференцијални дијагнози.

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IN MEMORIAM

DR ALI MEHMEDI 1956-2019

Ali Mehmedi

Dr Ali Mehmedi, u lind më 12 Mars 1956 në f. Shitovë Kërçovë. Rrjedh nga një familje intelektualësh. Shkollën fillore dhe të mesme i kreu në Kërçovë. Studimet e mjekësisë në Universitetin Shën Kiril dhe Metodi në Shkup ku dhe diplomoj në vitin 1983.

Pas diplomimit u punësua si mjek i praktikës së përgjithshme në Qendrën Mjekësore Kërçovë .

Në vitin 2000 fillon me specializimin Pediatri të cilën me sukses e kryen në vitin 2004. Punoj në repartin e pediatrisë pranë Spitalit të përgjithshëm Kërçovë deri në ndarje nga jeta.

Pas specializimi ka kryer disa trajnime dhe specializim nga lëmin e Pediatrisë dhe Farmacisë në vend dhe jashtë si ai në Universitetin e Lubjanës 2015. Ishte anëtarë i Shoqatës të Mjekëve shqiptar dhe asociacioneve të tjera , si të Dhomës të Mjekëve në RM.

Dr Ali Mehmedi , në punën e tij profesionale si mjek dhe specialist u dallua si punëtor i palodhshëm për zellshmëri, korrektësi dhe profesionalizëm. Në kujtesën tonë do të mbetet si vëlla, kolegë, humanist, shok, besnik dhe dinjitoz.

Ndërroj jetë 20.08.2019

Lavdi.

Përgatiti : Prim Dr Ilmi Mehmedi

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prezantim rasti apo kumtesë e shkurtër – deri 6 faqe dhe maksimum 3 tabela dhe/ose figura/imazhe.

Letër redaksisë - deri 2 faqe

Së bashku me dorëshkrimin, dorëzoni një faqe me **titullin** e artikullit; **emrin/at e autorit/ve**, duke përfshirë emrin me jo më shumë se dy tituj shkencor; emrin e departamentit dhe institucionit në të cilin është bërë punimi; institucioni ku punon (për secilin autor); si dhe emri dhe adresa e autorit të cilit do ti adresohen kërkesat nga ana e Redaksisë (shihni Informacionet plotësuese për autorët)

Abstrakti duhet te jete me jo më shumë se 250 fjalë. Duhet të konsistojë në katër paragrafë, i klasifikuar në Hyrje, Metodat, Rezultatet dhe Diskutimi (Përfundimet). Ato duhet të përshkruhen shkurt, respektivisht, problem qenësor i studimit, se si është kryer studimi, rezultatet e fituara, dhe perfundimi.

Tabelat, figurat dhe legjendat (shihni Informacionet plotësuese për autorët)

Fjalët kyqe -Tri deri pesë flaje apo fraza te shkurtëra duhet t'i shtohen pjesës së fundme të faqes së abstraktit.

Citatet e referencave në tekst duhet fillimisht të jenë nga revistat e indeksuara në **PubMed**. Stili i referencave që kërkohet nga Medicus është i formatit Vancouver (shihni Informacionet plotësuese për autorët).

Shkurtimet (**akronimet**) përdoren për njësitë matëse, kurse në raste tjera kur përmendet për herë të parë, ai duhet të jetë i sqaruar me fjalën bazë bashkangjitur.

Për të gjitha barnat duhet të përdoren **emrat gjenerik** ndërkombëtar. Nëse në hulumtim janë të përdorura brendet e patentuara, përfshini emrin e brendit në kllapa në paragrafin e Metodave.

Dorëshkrimi i dërguar tek botuesi duhet të shënohet nga autorët , nëse janë në seksionin e "punimeve origjinale shkencore" apo në pjeset tjera përmbajtesore të revistës.

Autorët marrin dy kopje të botimit përkatës.

The number of pages (including tables and/or figures/ illustrations) is dependent upon the type of the article:

original research paper - up to 12 pages and no more than 6 tables and / or graphs / pictures;

professional or review paper - up to 8 pages and no more than 4 tables and / or figures / images;

case report or brief communication - up to 6 pages and a maximum of 3 tables and / or figures/images.

Leter up to 2 pages

With the manuscript, provide a page giving the title of the paper; the name(s) of the author(s), including the first name(s) and no more than two graduate degrees; the name of the department and institution in which the work was done; the institutional affiliation of each author; and the name and address of the author to whom reprint requests should be addressed. (see Additional Information for Authors)

Provide an **abstract** of not more than 250 words. It should consist of four paragraphs, labeled Backround, Methods, Results and Conclusions. They should briefly describe, respectively, the problem being in the study, how the study was performed, the salient results, and what the authors conclude from the results.

Tables, figures and legends (see Additional Information for Authors)

Three to five **key words** or short phrases should be added to the bottom of the abstract page.

Quotations of references in the text should primarily be from journals indexed in **PubMed** which have proven their significance. The style of references required by **Medicus** is the Vancouver format (see Additional Information for Authors).

Except for units of measurement, abbreviations are discouraged. The first time an abbreviation appears it should be preceded by the words for which it stands.

The international **generic names** should be used for all drugs. When proprietary brands are used in research, include the brand name in parentheses in the Methods section.

All manuscript sent to the editor should be noted by the authors whether they are meant for the "original research papers" section or the rest of the journal's content.

The authors receive two copies of the relevant issue.

Informacione plotësuese për autorët

I. Faqja e parë – *ballina*: Duhet të përmbajë: (a) titullin e punimit, të shkurtër, por informativ; (b) emri, inicialet e emrit të mesëm dhe mbiemrit të secilit autor; (c) institucioni; (d) emri i departamentit që i atribuohet punës shkencore; (e) emri dhe adresa e autorit për t'iu përgjigjur në lidhje me dorëshkrimin; (f) burimi/përkrahja në formë të granteve, paisjeve, barnave dhe në përgjithësi.

II. Faqja e dytë – *abstrakti dhe fjalët kyqe*: Abstrakti duhet të shkruhet me maksimum prej 150 fjalësh për abstraktet e pastrukturuara, dhe me 250 fjalë për abstraktet e strukturuara (pjesët përmbajtësore: objekti/ete studimit ose hulumtimit, procedurat bazë, siç është përzgjedhja e subjekteve apo kafshët laboratorike, metodat vrojtuese dhe analitike, pastaj, rezultatet/gjetjet përfundimtare (të dhënat dhe rëndësia e tyre statistikore, nëse është e mundur), dhe konkluzionet kryesore. Vini theksin mbi aspektet e reja dhe të rëndësishme të studimit apo vrojtimit. Nën abstraktin indentifikoni dhe shkruani fjalët kyqe: 3-5 fjalë apo fraza të shkurtëra që do të ndihmojnë në paisjen me tregues të punimit dhe publikimit të abstraktit. Përdorni terme nga lista e Index Medikus për Nëntituj Mjekësor (Medical Sub-Headings [MeSH]); nëse nuk ka term të përshtatshëm në MeSH për disa terme të reja, mund të përdorni termet e dhëna.

III. Faqja e tretë dhe të tjerat – *teksti i plotë i artikullit*: Teksti i plotë I artikujve hulumtues ose vrojtues normalisht, por jo domosdoshmërisht, duhet të jetë i ndarë në paragraf me këta nëntituj: hyrja, metodat dhe materialet, rezultatet dhe diskutimi.

1. Hyrja: Krijoni një kontekst apo prapavijë(trualli) të studimit (që në fakt është natyra e problemit dhe rëndësia e tij). Për të bërë këtë duhet të bëni një hulumtim të literaturës – duke kërkuar, gjetur dhe lexuar punimet përkatëse, që duhet të jenë si referencë në dorëshkrimin tuaj. Sqaroni hipotezat tuaja dhe planifikoni t'i testoni ato, si dhe përshkruani qëllimet tuaja. Kini qëndrim të qartë se çka prisni të gjeni dhe arsyet që ju udhëhoqën tek hipotezat që keni krijuar. Objekti i hulumtimit më së shpeshti fokusohet kur parashtrohet si pyetje. Mos përfshini të dhëna apo rezultate nga puna që do të raportohet.

2. Metodat & Materialet: Ky paragraf duhet të përfshijë atë informacion që ishte në dispozicion në kohën që plani apo protokoli i studimit po shkruhej. Të gjitha informacionet e marra gjatë studimit i takojnë paragrafit të Rezultateve.

Përshkruani përzgjedhjen tuaj të pjesëmarrësve së vrojtimit ose eksperimentit (pacientët ose kafshët laboratorike, përfshirë kontrollat) qartë, duke përfshirë kriteret e përshtatshme (inkluzive) dhe përjashtuese (ekskluzive).

Parimi udhëheqës duhet të jetë i qartë se si dhe pse studimi është bërë në një mënyrë të caktuar. Jepni detaje të mjaftueshme për metodat, mjetet dhe materialet (jepni emrin dhe adresën e prodhuesit në kllapa), dhe procedurat për të lejuar të tjerët të kuptojnë dhe riprodhojnë rezultatet tuaja.

Nëse një metodë e caktuar që është përdorur është e njohur, atëherë nuk është e nevojshme të jepet përshkrim komplet i saj. Mund t'i referoheni punimit në të cilin së pari herë është përshkruar dhe të

Additional Information for Authors

I. First page - *front page*: It should contain: (a) title of paper, a short, but informative; (b) the first name, initials of middle name and last name of each author; (c) the institution; (d) the name of the department that is attributable to the scientific work; (e) the name and address of the author with whom to correspond about the manuscript (f) source/support in the form of grants, equipment, drugs, or all.

II. Second page - *abstract and keywords*: The abstract should be written with a maximum of 150 words for unstructured abstracts and 250 words for structured abstracts (containing parts: objective(s) of study or research, basic procedures, such as selection of subjects or laboratory animals, observational and analytical methods, then, the main findings/results (data and their statistical significance, if possible), and the main conclusions. Emphasize the new and important aspects of the study or observation.

Below the abstract identify and write the keywords: 35 words or short phrases that will assist in indexing the paper and publication of the abstract.

Use terms from the list of Index Medicus for Medical Sub-Headings (MeSH); if there is no appropriate MeSH term for some newly introduced terms, we can use the given terms.

III. Third and further pages – *full text of the article*: The full text of research or observational articles should normally be, but not necessarily, divided into sections with the following headings: introduction, material and methods, results and discussion.

1. Introduction: Provide a context or background for the study (that is, the nature of the problem and its significance). To do this you must complete a literature review – searching for, finding and reading relevant papers, which must be referenced in your manuscript. Explain your hypotheses and the plan to test them, and describe your aims. Clearly state what you expect to find and the reasoning that led you to the hypotheses that you have made. The research objective is often more sharply focused when stated as a question. Do not include data or conclusions from the work being reported.

2. Methods & Material: This section should include only information that was available at the time the plan or protocol for the study was being written. All information obtained during the study belongs in the Results section.

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria.The guiding principle should be clarity about how and why a study was done in a particular way.

Give sufficient details of the methods, apparatus and materials (give the manufacturer's name and address in parentheses), and procedures to allow others to understand and reproduce your results.

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 dorëshkrimeve 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.

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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).